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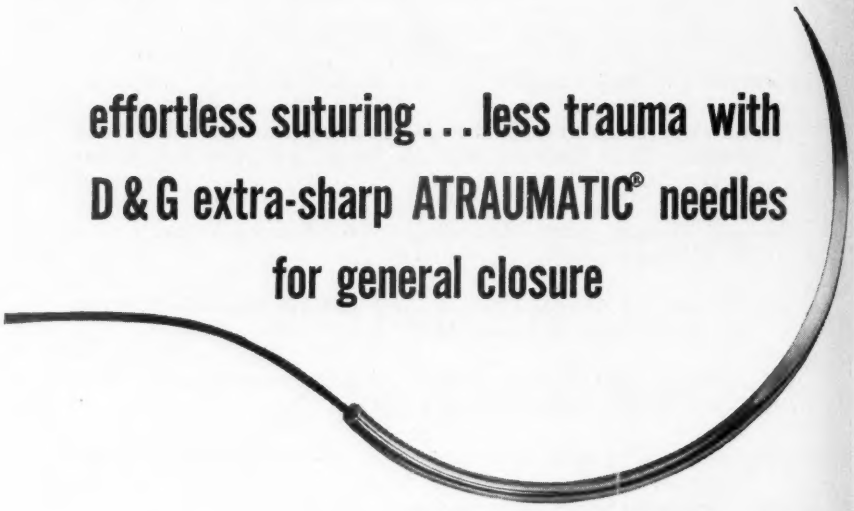

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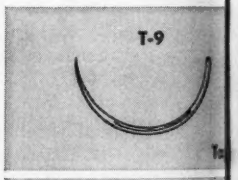


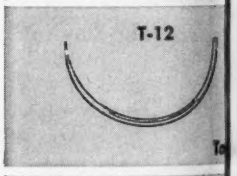


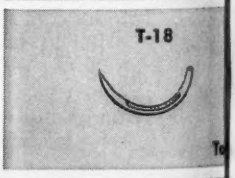


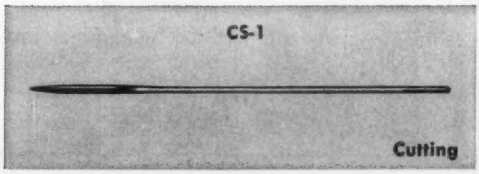


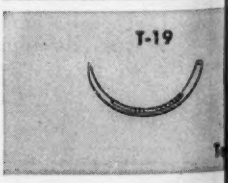

THE
AMERICAN
SURGEON

Vol. 20, No. 2 February, 1954

## FOREWORD

The story of medical education in Colorado is a long and interesting one. The Denver College of Medicine, under the auspices of the University of Denver, was organized in 1881. Two years later in 1883, the Gross Medical College and the Colorado School of Medicine were started, and one year later, 1884, the Denver Homeopathic College was organized. This latter institution after several reorganizations became extinct in 1909. In 1902 the Denver College of Medicine and the Gross Medical College united to form the Denver and Gross College of Medicine and the Medical Department of the University of Denver. In 1911 this institution was absorbed by the University of Colorado School of Medicine. Since 1911, therefore, the University of Colorado School of Medicine has been the only medical school in the state.

The University's first degrees in medicine were awarded in 1885 on the basis of a two-year course. In the early nineties the course was advanced to three years. In 1897 the University attempted to move the clinical years to Denver but the effort was delayed for a time due to an injunction obtained by the Denver and Gross College of Medicine and, as a result, the University did not have any graduates in medicine in 1898 or 1899. It was not until 1908 that an amendment to the constitution made it possible for the University to give the clinical years of medicine in Denver.

The union of the Denver and Gross and University schools was largely the result of the Flexner Survey of Medical Education which was published in 1910. In this year the University moved the junior and senior classes to Denver and the medical course was lengthened to four years. The Denver General was the teaching hospital. Nineteen hundred and thirteen was the last year when medical students were selected from high school.

In 1923 a measure initiated to prevent animal experimentation was defeated at the polls. About the same time the University began negotiations with the Rockefeller and Carnegie Foundations which ultimately resulted, together with legislative appropriations and many gifts from local citizens, in the present physical plant which the medical school and hospitals occupy today.

Before all four years of the medical school could be moved to Denver it was necessary that the constitution be amended further. This had been done in 1921. The first medical students were brought to the new campus in 1924. The Psychopathic Hospital was opened in the same year and a little later the Colorado General Hospital opened its doors.

Nineteen hundred and twenty-five found the clinical teaching being done entirely, except for psychiatry, by volunteer practicing physicians. Provisions for clinical research were nil. These deficiencies were not overcome until after World War II when a combination of remodeling and new construction resulted in the addition of research and administrative space and facilities for a full-time clinical faculty. Facilities and space for expanded research in the preclinical areas were also added.

The full-time faculty was gradually increased in size and improved in balance so that the point has now been reached where each department of the Medical School is able to conduct a program that is well balanced as between undergraduate and graduate teaching, service and research—all well integrated so that each is complementary to the other.

In 1946 the undergraduate curriculum was completely overhauled and at the same time machinery was set up so that curricular revision and indicated changes would always be possible. The constant aim of the teaching program for the undergraduate student has been to present medicine as a practical facet of general human biology. The effect is to lead the student to appreciate the importance of the patient as a total human organism; to believe that good medical care is really good patient care. The education of graduate students, research, and service are subservient to this general aim, but while subservient, they are still recognized as essential. This is because of the realization of the fact that if competent teachers are to be obtained and retained, each must have stature in at least one of the many scientific fields—clinical as well as preclinical—that go to make up the whole of medicine. In other words it is believed that it is essential to good undergraduate teaching that each of the medical sciences be presented as a part of general medicine. In order to have teachers capable of doing this, it is important that these teachers have outlets and opportunities that will maintain their stature in their respective scientific fields. Service to patients, research, the teaching of advanced students, the attendance and participation in medical scientific meetings and the preparation of research and scientific papers are essential to this stature.

This issue of *The American Surgeon* represents an appreciated opportunity for the surgical faculty of the University of Colorado School of Medicine to demonstrate its interests and capacities in research and scholarly work. The Regents and Administration of the University are proud of this fact and of this number of *The American Surgeon* and of its significance as far as the recognition of the faculty is concerned.

WARD DARLEY, M.D.
*President,*
*University of Colorado*

# THE BEDSIDE CLINIC AND LABORATORY IN THE MANAGEMENT OF ACUTE DEHYDRATION

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*Denver*

## INTRODUCTION

Evaluation of the water, electrolyte and blood needs of the acutely dehydrated individual constitutes a frequent problem in the practice of surgery. The most frequent situation posing this problem is intestinal obstruction. Patients suffering with acute small bowel obstruction are usually first seen after several hours to several days of vomiting. Thus, the physician is faced with a patient who needs a major surgical procedure and who frequently is dehydrated and depleted of electrolytes. Usually the physician is seeing the patient for the first time and no information as to the patient's cardiovascular and renal status is available except that which can be determined at the time by history, physical examination, and laboratory studies. To establish the optimum time to operate upon these patients, and to give the proper amount of water and electrolyte replacement before operation, requires mature clinical judgment and as much information as possible about the patient's general health and current physiologic status.

The treatment of small bowel obstruction, in the vast majority of cases, we think should be operative. It is not our custom to rely on intestinal intubation as definitive therapy. However, we have found intubation a very useful *holding operation* while we are involved in the preparation of the patient for surgical intervention. Patients with intestinal obstruction of short duration will require very little in the way of fluid and electrolyte replacement and can be operated upon almost immediately after admission to the hospital. Thus, parenteral therapy, while on the operating table and immediately thereafter, will usually suffice to avoid serious electrolyte imbalances. Such a minor degree of water and electrolyte depletion will be obvious upon the initial examination of the patient. In most patients, however, extensive depletion will be present. We believe in early operation. But, the point that we wish to emphasize is that a preoperative critical evaluation of the patient with regard to his water and electrolyte status must be made and suitable replacement accomplished *before operation*.

The plan of management of patients depleted of water and electrolytes that we follow includes the use of some relatively simple, but fairly accurate *bedside* laboratory determinations which, correlated with an adequate history and physical examination, serve very well in evaluating the patient's needs for water and electrolytes. This plan has been used successfully by the intern and resident staff.

## THE HISTORY AND PHYSICAL EXAMINATION

In itself, the *history* relative to the current illness should yield sufficient data for the inquiring physician to establish the etiology of the dehydrated state.

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Further questioning should bring forth those pertinent points which form the groundwork for accurate estimation of total body losses of water and electrolytes. We have found the following guide to be useful in this regard:

1. Duration of symptoms.
2. Normal weight.
3. Frequency, number, and estimated volume of emesis and/or liquid stools.
4. Abnormalities of sweating.
5. Frequency of urination and quantity of urine.
6. Thirst.
7. Dryness of mucous membranes.
8. Lassitude or syncope.

Corroboration of the clinician's impression from the elicited history is secured by *physical examination* of the patient. When such an examination includes the following points, the subsequent laboratory determinations assume their rightful position, i.e., they become confirmatory and quantitative rather than diagnostic, and add to the accumulating mass of information about the patient.

1. Admission weight.
2. Presence of hyperpyrexia.
3. Hypotension.
4. Tachycardia, with weak peripheral pulsations.
5. Moisture of skin and mucous membranes.
6. Loss of normal ocular tension.
7. Acetone breath.
8. Loss of normal skin turgor.

## THE BEDSIDE LABORATORY

The essential laboratory determinations for management of these patients can be done by the attending physician, at the bedside, without the help of a clinical laboratory. Most of these tests are well known to the physician and have been made by him since his student days. These are: (1) the urinalysis, including measurement of urinary volume; (2) hematocrit; and the (3) white blood cell count and the differential count. Other tests, less generally done but very important, are bedside determination of: (1) plasma chlorides, (2) urinary chlorides, and (3) plasma carbon dioxide combining power.

## THE URINALYSIS

The urinalysis is of special value in the evaluation of the fluid and electrolyte situation of a patient. Not only is the initial urinalysis of importance but serial determinations will reflect the response of the kidneys to the fluid replacement therapy and thus point out adequacy of therapy and also the functional ability of the kidneys. *The total volume of urine excreted* is significant and should be measured and recorded accurately. Once therapy has been started and the urinary output should be noted and recorded at frequent intervals. In the extremely dehydrated patients we frequently *insert a retention catheter in the urinary bladder and record hourly urinary output.* A rising urinary output usually indicates that a state of more satisfactory hydration is being reached.

The determination of the *specific gravity* of urine is equally important. If, when the patient is seen initially, the urine volume is low and the specific gravity is high there is good reason to believe that kidney function is adequate and that the high specific gravity indicates dehydration. However, if a patient is seen who appears on physical examination to be dehydrated yet the specific gravity of his urine is low (near 1.010), poorly functioning kidneys must be suspected and replacement therapy must be given very cautiously and further studies must be done to determine more thoroughly the status of the kidneys (blood urea nitrogen, creatinine). Subsequent determinations of the urine specific gravity as treatment progresses are of prime importance. In the very severely dehydrated individual we determine the specific gravity of the urine every hour during the period that fluid is being replaced. A falling specific gravity of the urine, especially if coupled with a rising hourly urinary volume, usually indicates that hydration is being accomplished. *However, it must be remembered that even a dehydrated patient will not always retain water given intravenously if his extracellular fluid does not contain enough sodium. Also, if glucose in water solution is given too rapidly intravenously a glucose diuresis will result and dehydration may actually be increased.* These facts must be kept in mind when a patient receiving glucose in distilled water intravenously begins to show a marked increase in urinary output and/or a falling urinary specific gravity.

The determination of *glucose in the urine* is of importance in the management of fluid problems for several reasons. If glucose is present in the initial urinalysis, *and it is known that the patient has not received glucose intravenously recently,* the suspicion of diabetic acidosis as a factor (either completely or partly) in the cause of the dehydration must be raised. Repeat determinations of urinary glucose during administration of intravenous fluids are of value because, if the concentration of glucose in the urine is found to be persistently very high (3 or 4 plus), the rate of administration or the glucose concentration of the fluids being administered should be reduced to avoid the glucose diuresis described above.

Determination of *acetone bodies in the urine* is also important because their presence in the urine is a frequent finding in dehydration and/or carbohydrate starvation. This usually responds to treatment with the first 1 or 2 liters of fluid given. Of course, the finding of acetone bodies with glucose in the urine on initial analysis is strongly suggestive of diabetic acidosis as the cause of dehydration.

The *pH of the urine* is for the most part established by the relative quantities of monobasic sodium phosphate (acid in reaction) or dibasic sodium phosphate (basic in reaction) that are being excreted. These salts are excreted in an attempt to maintain normal plasma pH, and represent a crucial compensatory mechanism in acid-base balance. The urine is normally acid (except during the normal *alkaline tide* which occurs occasionally after meals). If the patient has relatively normal kidney function and has no urinary tract infection (which may produce alkaline urine) the reaction of the urine by and large indicates the general acid-base balance of the plasma. Thus, if the noninfected urine is alkaline in reaction it can be assumed with reasonable certainty that an alkalosis (compensated or uncompensated) exists in the plasma, and this information can be correlated with the carbon dioxide power of the plasma to further evaluate the situation. A high

carbon dioxide combining power associated with alkaline urine usually means metabolic alkalosis, and a low carbon dioxide combining power associated with alkaline urine probably means a respiratory alkalosis.

The determination of *albumin* in the urine with the microscopic study of the urinary sediment may point to the presence of renal disease, and thus the need for caution in fluid and salt administration.

## METHODS AND EQUIPMENT FOR THE URINALYSIS

The equipment necessary for determining urinary volume needs no description. Measurement of the volume of the initial urine specimen can be done with any convenient calibrated receptacle. For the determination of hourly urinary volume we place a large graduated cylinder (1,000 ml. capacity) near the bedside and allow the urine from the retention catheter to run into the cylinder. The level can be noted hourly, thus furnishing a method of measuring hourly volume without actually pouring the urine from one container to another (unless removed for specific gravity determinations).

We determine the urine specific gravity with the standard hygrometer manufactured for the purpose and purchased quite inexpensively. It is pictured with the remainder of the bedside laboratory equipment.

Qualitative urinary glucose determinations can be done very easily using either Benedict's solution (described in any clinical laboratory manual) or by using the convenient Clinitest* tablets. We find the latter to be time saving and quite satisfactory. Determination of acetone bodies in the urine can be made by the standard procedures (sodium nitroprusside for acetone and ferric chloride solution for acetoacetic acid). However, we have found the use of Acetest* tablets accurate enough and time saving. Complete directions for the use of the Acetest as well as the Clinitest tablets are included in the information supplied with each bottle of the tablets.

The reaction of the urine can be quickly ascertained by the use of litmus paper, or if desired the diphenylcarbazone solution used as an indicator for the chloride determinations (described later) can be used by merely adding a few drops of the indicator to a few cubic centimeters of urine. This indicator is red when alkaline and yellow when acid. We use litmus paper for this test unless we are also determining chloride concentration of the urine, in which event we note the reaction of the urine when the indicator is added to the urine, before the addition of other reagents.

The determination of albumin in the urine can be done by several methods all of which are described in standard laboratory texts. We use Bumintest† which we find quite satisfactory and simple to use. The complete directions for the use of this reagent are furnished with each bottle.

The microscopic study of the urinary sediment needs no description. The necessary equipment is a centrifuge, a microscope slide, and a microscope.

* Ames Company, Inc., Elkhart, Ind.
† Ames Company, Inc., Elkhart, Ind.

### THE WHITE BLOOD CELL COUNT AND DIFFERENTIAL WHITE BLOOD CELL COUNT

The white blood cell count and the differential are of the same importance in these cases as in any other surgical emergency. It does not seem necessary to obtain a red blood cell count and hemoglobin determination since the hematocrit furnishes a fairly reliable estimate of the red blood cell concentration.

The technic of doing a white blood cell count and differential needs no description—the technic is described in any clinical pathology textbook. The equipment is standard.

### THE HEMATOCRIT DETERMINATION

Determination of the hematocrit is easily done very accurately, and furnishes much information about the state of hydration of the patient as well as an estimate of his need for transfusion of whole blood. The initial hematocrit is important, but once again, subsequent determinations done during the course of hydration will be of more value. As hydration is accomplished the hematocrit reading will fall, thus indicating adequacy of therapy. If, as hydration progresses, the hematocrit falls to readings below normal the need for whole blood replacement becomes obvious. We have seen severely dehydrated patients whose hematocrits were in the neighborhood of 60 to 65 per cent upon admission. Serial hematocrits done during hydration revealed steadily falling values. When the urinary output and specific gravity, with the clinical appearance of the patient, indicated that hydration was accomplished the hematocrit readings were in the neighborhood of 30 to 40 per cent, indicating the need for whole blood.

Hematocrit determination is a very simple procedure, and if done carefully a very accurate one. Venous blood is drawn from a good-sized vein without a tourniquet around the extremity. The needle may be introduced into the vein with a tourniquet in place, but before the blood is drawn the tourniquet should be removed and blood allowed to flow in the vein freely. The blood is then transferred from the syringe into a heparinized test tube and agitated. Citrate should not be used because sometimes crenation of the cells occurs and slightly changes the results. Next, the heparinized blood is transferred to each of two Wintrobe hematocrit tubes, filling to the 0 mark. This transfer is best done by the use of a long spinal tap needle which will allow filling the hematocrit tube from the bottom up, without formation of air pockets in the small lumen hematocrit tube. The tubes are then balanced against each other in a table centrifuge and spun at top speed for 30 minutes; they are then removed and the readings on each tube taken. They are then allowed to spin another 10 minutes in the centrifuge and read again. If no change has occurred in the readings this is taken as the final reading. If the test has been done properly the readings of the two tubes should agree closely.

### THE BEDSIDE DETERMINATION OF PLASMA CARBON DIOXIDE COMBINING POWER AND PLASMA CHLORIDES

The value of determination of the plasma carbon dioxide combining power and the plasma chlorides is well known. In many hospitals, however, this infor-

mation is not always available. We present methods for making these determinations which can be done by the physician at the bedside. The interpretation of these determinations in relation to our regime of management of acute dehydration will be discussed later. Although these are two separate determinations they are done serially in the same flask using the bedside testing kit and for that reason are considered together.

### THE BEDSIDE DETERMINATION OF PLASMA CARBON DIOXIDE COMBINING POWER AND PLASMA CHLORIDES

In 1950 Scribner[3, 4] described methods for determining serum chloride concentration and serum carbon dioxide combining power at the bedside. We have elected to simplify his methods somewhat with a resulting slight loss in accuracy of the carbon dioxide combining power. However, our method is well within the limits of accuracy for successful therapy, and, we think, benefits from the ease of performance.

The equipment and reagents necessary for these bedside determinations are easily available to any physician and consist of:

*Glassware*

4—60 cc. dropper bottles with caps
2—30 cc. dropper bottles with caps
4—1 cc. tuberculin syringes
1—50 cc. Ehrlenmeyer flask

*Needles*

1—short 25 gauge needle

*Reagents* (To be *accurately* prepared or procured by a pharmacist)

0.1 N Sodium Hydroxide (500 cc.)
0.1 N Nitric acid (500 cc.)
Solution of mercuric nitrate ($Hg(NO_3)_2 \cdot H_2O$), 17.13 Gm. per liter of distilled water, with 2 cc. of concentrated nitric acid added (500 cc.).
Diphenylcarbazone, 120 mg. in 130 cc. of 95 per cent ethyl alcohol. Phenolphthalein, 150 mg. in 30 cc. of 95 per cent ethyl alcohol; 0.1 N Hydrochloric acid (to standardize sodium hydroxide and mercuric nitrate solutions) (500 cc.).

The droppers are removed from the four 60 cc. bottles and the tops cut off the dropper bulbs. The tuberculin syringes are inserted into the caps so as to hang down into the bottles. The bottles, so equipped, are filled with: (1) distilled water (for the sample syringe), (2) 0.1 N sodium hydroxide, (3) 0.1 N nitric acid, and (4) the mercuric nitrate solution.

The two 30 cc. dropper bottles are filled with the indicators, the diphenylcarbazone and phenolphthalein. After the bottles are properly labeled they are assembled as illustrated (fig. 1).

### STANDARDIZATION

Standardization of all of the reagents and the tuberculin syringes must be done initially and periodically (by the physician or pharmacist). It is done by using

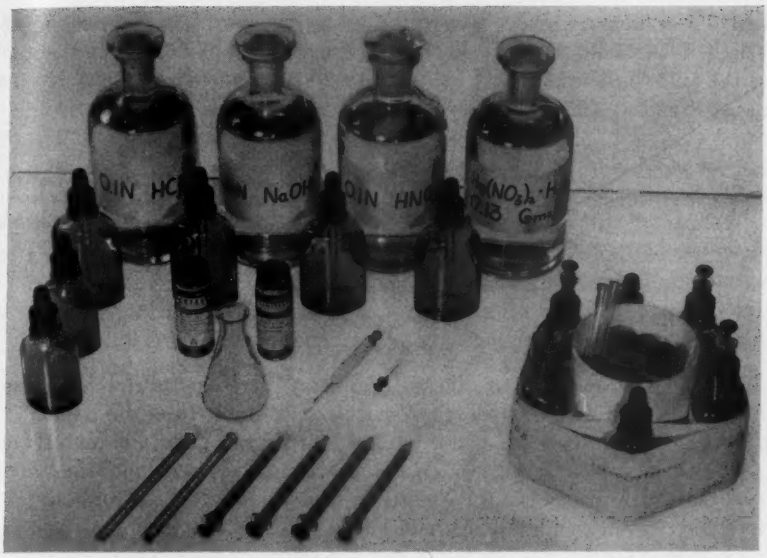


FIG. 1. The necessary equipment with the stock solutions for the *bedside laboratory* can be seen on the left of the picture, while the assembled unit is on the right. Note the compact size and easy portability of this laboratory.

the 0.1 N hydrochloric acid as the standard solution. The sample syringe is filled to the 1 cc. mark with the 0.1 N hydrochloric acid. The contents of this syringe are then placed in the Ehrlenmeyer flask, and 3 drops of the diphenylcarbazone are put in the flask. Next the mercuric nitrate syringe is filled to the 1 cc. mark and the solution titrated into the flask until a purple end point is reached. If this has required exactly 1 cc. of the mercuric nitrate the concentration of this solution is correct. If it has required less than 1 cc. of mercuric nitrate the solution must be adjusted by the addition of water; that is, if 0.92 cc. were used then 920 cc. of the mercuric nitrate solution should be taken and distilled water added to make 1000 cc. If more than 1 cc. of the mercuric nitrate solution is required to reach the end point then a small quantity of the powdered mercuric nitrate should be added to the stock solution until less than 1 cc. is required to reach the end point; then the adjustments as described above are done. For standardization of the sodium hydroxide solution again 1 cc. of the hydrochloric acid is added to the Ehrlenmeyer flask and 3 drops of the phenolphthalein solution are added. Then the sodium hydroxide syringe is filled to the 1 cc. mark and titrated into the flask. This should require 1 cc. to reach the *faint* permanent pink end point. If the required quantity to reach the end point is not exactly 1 cc. then a similar procedure as described for the mercuric nitrate solution standardization should be used. It must be determined how much of the 0.1 N nitric acid is necessary to react with 1 cc. of the standardized sodium hydroxide. One cc. of the nitric acid is placed in the Ehrlenmeyer flask and 3 drops of phenophthalein solution are

added. The sodium hydroxide syringe is filled to the 1 cc. mark and titrated into the flask. This should require 1 cc. to reach the pink end point. If such is not the case the following formula may be used to ascertain the volume of 0.1 N nitric acid needed to neutralize exactly 1 cc. of the standardized sodium hydroxide.

$$\text{(a)}\quad \text{Vol. of 0.1 N nitric acid needed} = \frac{1.0}{\text{Vol. of 0.1 N sodium hydroxide used}}$$

This volume of nitric acid will then be used in all subsequent determinations. *Standardization should be made every month or when any of the solutions or syringes are replaced.*

### METHOD FOR DETERMINATION OF CARBON DIOXIDE COMBINING POWER AND OF PLASMA CHLORIDE

The determination of carbon dioxide combining power and of chloride is made as follows: A 4 or 5 cc. sample of venous blood is drawn from the patient and placed in an oxylated tube, stoppered and centrifuged. Plasma is immediately drawn into the sample syringe to the 1 cc. mark and discharged into the Ehrlenmeyer flask. The volume of 0.1 N nitric acid determined in the formula (a) is drawn into its tuberculin syringe and added to the contents of the flask. The flask is swirled for two minutes and allowed to stand for one minute. Three drops of phenolphthalein indicator are then added. The 0.1 N sodium hydroxide is then drawn into its syringe to the 1 cc. mark and is titrated into the flask to the permanent pink end-point. With the no. 25 gauge needle on the syringe, each drop will equal .01 cc. (or 1 mEq.). The quantity of sodium hydroxide *remaining in the syringe* is read in hundredths of a cc. *This figure represents the carbon dioxide combining power of the sample in milliequivalents per liter.* Next, the contents of the flask are acidified by the addition of 1 cc. of the 0.1 N nitric acid and 3 drops of the diphenylcarbazone indicator are introduced. The mercuric nitrate solution is drawn to the 1 cc. mark in its syringe and titrated into the flask until the purple end point is reached. The quantity of mercuric nitrate solution *used* is determined in hundredths of a cc. *This figure represents concentration of chloride in the sample in milliequivalents per liter.*

### DETERMINATION OF URINARY CHLORIDE

A decreased quantity or an absence of chloride in the urine may be the first indication of salt depletion, since urinary chloride output usually drops before the plasma chloride falls. However, one situation in which a low plasma chloride (combined with a high plasma carbon dioxide power) is associated with a high concentration of chloride ions in the urine is in an occasional case of potassium deficiency. We have been able to diagnose potassium deficiency several times by this combination of findings. In these cases the low plasma chloride level does not respond to treatment with sodium chloride or ammonium chloride solutions given intravenously until potassium chloride is also given. Since the determination of serum or plasma chlorides, carbon dioxide combining power, and urinary chlorides is easily done with the bedside test, whereas the determination of serum

potassium is a rather involved laboratory test sometimes not even available, the detection of potassium deficiency by this method becomes doubly important.

### METHOD FOR DETERMINATION OF URINARY CHLORIDE

*The urinary chloride concentration* can be quickly and easily determined by using the same bedside testing set used for the serum chloride test. The test is done in the same manner as the serum determination—1 cc. of urine is measured into the flask with the sample syringe, it is acidified by the addition of 1 cc. of the 0.1 N nitric acid, a few drops of diphenylcarbazone are added and titration is done with the mercuric nitrate solution. The reading of the test is the same—every hundredth of a cc. of solution used to reach the end point equals 1 milliequivalent of chloride per liter of urine. This test is usually done on an aliquot of the 24 hour urine sample.

### PLAN OF THERAPY

The first consideration is to establish a definite period of time which will be allotted to hydration and correction of electrolyte disturbances. It will be the shortest time consistent with the attainment of adequate repair and will vary with each patient. Many factors, such as the nature of the patient's primary illness, the degree of dehydration and electrolyte imbalance, and the status of the patient's cardiovascular system, will influence the determination of this period. Nevertheless, a definite period should be selected at the end of which time operation is planned for the definitive surgical correction of the primary disease at minimal risk in an adequately prepared patient. This period may vary from 2 to 48 hours; however, usually it will be in the neighborhood of 12 to 18 hours. During this period of *repair* other procedures are done as indicated, such as intestinal intubation, and administration of antibiotics. Obviously developments during the *repair period* may alter plans. Signs of development of strangulation may appear in the process of preparing the patient for operation to relieve small bowel obstruction and force the surgeon to consider earlier operation than he had planned. On the other hand, intestinal intubation may relieve intestinal obstruction during the *repair period* and make operation unnecessary.

In the following paragraphs our plan of therapy will be found to contain many formulas, and mathematical discussions. We do not wish to convey the idea that we believe that this is a mathematically precise science—and we apologize for the type of presentation in advance. The formulas, however, are given in an explanatory fashion, and attempt to point out rationale in therapy. It is not our purpose to present a fool-proof, accurate, precise method for calculating fluid and electrolyte deficit—we know of none.

Two major requirements must be satisfied in replacement therapy during this *repair period:* (1) deficit must be replaced, and (2) maintenance needs during the repair period must be met. Replacement and maintenance also can be considered conveniently in four categories: (1) water, (2) chloride, (3) sodium, and (4) potassium.

### WATER

(1) *Deficit to be replaced:* It is generally stated that signs of clinical dehydration are not evident until a quantity of water equal to about 5 per cent of body weight has been lost. This serves as an excellent starting point in water replacement. We, therefore, divide patients into three categories for the purpose of water replacement: (a) patients with a history of vomiting and/or diarrhea but with no clinical evidence (or very minimal evidence) of dehydration (replace water in the amount of 4 per cent of body weight), (b) patients with moderate clinical evidence of dehydration (replace water in the amount of about 6 per cent of body weight), and (c) patients with severe evidence of dehydration (administer water in amount of 8 per cent or more and re-evaluate for need for additional water).

(2) *Maintenance during the "repair period":* All obvious loss of fluid during the repair period should be replaced in equal quantity and an additional quantity of water should be given for urinary excretion and for replacement of insensible loss:

1. Replace gastric suction, vomitus, and liquid stools (equal quantities).
2. Water for urinary excretion—1000 cc. for 24 hour period.
3. Insensible loss (skin and lungs)—800 cc. to 1500 cc. for 24 hour period.

For example, using this scheme, if a man weighing 50 Kg. enters the hospital with a history of vomiting for two days as a result of intestinal obstruction and shows signs of clinical dehydration on examination his immediate water need will be 3,000 cc. (6 per cent of 50 Kg.). If nasogastric suction is instituted and a period of 12 hours is decided upon as a *repair period* before operation, then additional water will be needed. If nasogastric suction during this 12 hour period amounts to 1,500 cc. then:

| | |
|---|---|
| Immediate need to correct dehydration | 3,000 cc. |
| Water for urinary excretion (12 hours) | 500 cc. |
| Insensible loss (12 hours) | 750 cc. |
| Gastric suction loss | 1,500 cc. |
| Water to be given before operation | 5,750 cc. |

Obviously the 1,500 cc. of gastric suction cannot be anticipated at the beginning of the 12 hour period. By re-evaluating the situation every two or three hours and readjusting the fluid intake to compensate for the quantity of gastric loss it is possible to deliver the proper intake of water within the allotted time. Also, the hematocrit, urinary volume, urine specific gravity and the patient's response to the fluids may indicate that the original estimate of 6 per cent of body weight was in error (and readjustments may have to be made during the repair period).

### CHLORIDES

(1) *Chloride deficit to be replaced:* Extracellular water is generally stated to account for approximately 20 per cent of body weight.[1] It accounts for less in extremely obese individuals.[2] Chloride is for the most part an extracellular ion. Therefore, 20 per cent of body weight times the chloride in 1 liter of plasma

roughly equals the total body chloride. Also, since the normal plasma chloride (and the normal chloride in extracellular fluid) is 103 mEq./L 20 per cent of body weight times 103 equals the normal total body chloride (in mEq.). Therefore, if the mEq. of chloride per liter of the patient's plasma is determined the deficit of chlorides can be calculated. The formula for calculation of chloride deficit is derived therefore as follows:

(b) $\frac{\text{Body Wt. in Kg.}}{5} \times (103 \text{ minus patient's } Cl^-/L)$

$= \text{chloride deficit in dehydrated state.}$

However, the quantity of fluid that is to be introduced into the patient must also enter into the calculations. The figure generally stated for total body water is 70 per cent of body weight.[1] However, Moore[2] has shown that this can vary from 45 per cent to 70 per cent, depending upon the age, sex and habitus of the patient. For the purpose of these calculations it seems reasonably accurate to assume that the extracellular fluid comprises approximately one-third of the total water. Therefore, one-third of the water *given to replace deficit* will enter the extracellular space and should be considered as an increase in the extracellular compartment. This assumption may be somewhat in error since the distribution of fluids through the various compartments making up the total body water (intravascular, interstitial, and intracellular) is controlled for the most part by osmotic pressure in the various compartments, and since the work of the kidneys cannot be anticipated these calculations can only be used as a starting point in treating the patient. However, we have found the following formula for replacing chloride deficit to be quite usable and often reasonably accurate. It is to be noted that in addition to the chlorides for replacement of deficit as calculated in the formula given above (b) an additional amount of chloride is supplied to take care of the dilution of the extracellular compartment by one-third of the water retained. Since *the water given to repair deficit* is the amount which has been estimated to be sufficient to return the patient to normal hydration, this amount is considered a *water retained* for the purposes of this formula. The number of liters of fluid given *to repair deficit*, therefore, is divided by 3 and the result multiplied by 103 (the number of mEq. of chloride in 1 liter of extracellular fluid). Adding this quantity to the previously calculated deficit gives the formula:

(c) $\frac{\text{Body Wt. in Kg.}}{5} \times (103 \text{ minus patient's } Cl^-/L) \text{ plus } \frac{\text{Liters } H_2O \text{ retained}}{3}$

$\times 103 = \text{chloride needed for repair to normal hydration (mEq.).}$

(2) *Maintenance of chlorides lost during repair period:* In addition to the chlorides replaced for existing deficit they also must be given for loss during the period. Average figures for chloride concentration in various fluids are available. However, it seems more rational to determine the quantity of chloride actually being lost via various routes (gastric suction, bile, small bowel suction, etc.) and replace that quantity. *This can be done quickly by the use of the bedside testing kit.*

Loss of chlorides via the urinary excretion route is usually negligible during times of chloride depletion except in rare instances, such as may occur in the presence of a coexisting potassium deficiency. However, it seems wise to conduct chloride determinations on the urine (24 hour specimen) with the bedside set.

Average values of chloride concentration (in mEq./L) in various body fluids are:

| | |
|---|---|
| Gastric suction | 90 mEq/L |
| Small bowel suction | 100 mEq/L |
| Bile (fistula) | 100 mEq/L |

Thus, total chloride necessary to give to a patient in the repair period:

(1) calculated deficit, plus

(2) calculated loss during repair period.

The original estimate of chloride deficit can be given in the first fluids in the repair period and subsequently the remaining chloride needs can be satisfied during the later hours of the period as measurements of loss are made.

In the light of this discussion, let us return to the example of the patient discussed above who had suffered from two days of vomiting as a result of intestinal obstruction. We have already estimated that he needs 5,750 cc. of water. To calculate his chloride needs in the same period we can use the above plan if the plasma chloride determination is made upon the patient's admission to the hospital. For example, if his plasma chloride was determined to be 87 mEq/L, his weight 50 Kg., and the water he is to receive parenterally 5,750 cc. (3,000 to repair deficit plus 2,750 for maintenance and loss during repair period), then

$$\text{(c)}\quad \frac{\text{Body Wt. in Kg.}}{5} \times (103 \text{ minus patient's } Cl^-/L) \text{ plus } \frac{\text{Liters } H_2O \text{ retained}}{3} \times 103 = \text{chloride needed for repair to normal hydration (mEq.).}$$

By substitution in the formula:

$$\frac{50}{5} \times (103 \text{ minus } 87) \text{ plus } \frac{3.0}{3} \times 103 =$$

or $(10 \times 16)$ plus $(1.0 \times 103)$ =

or 160 plus 103 = 263 mEq. chloride necessary to replace deficit.

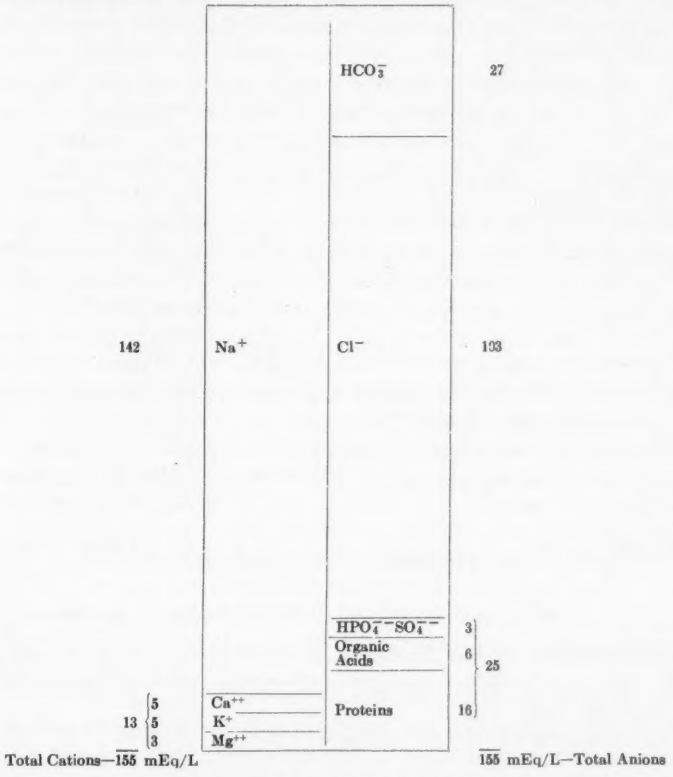
Then to complete the example: The patient lost 1,500 ml. of gastric suction in the repair period. Since gastric suction contains about 90 mEq/L then 90 times 1.5 should equal millequivalents of chloride necessary to replace loss during *repair period*. Thus, 90 times 1.5 or 135 mEq. of chloride is added to the 263 mEq. already calculated and the patient should be given 398 mEq. of chloride.

### SODIUM

The problem of replacement of sodium is similar to that of chloride replacement in that they are both for the most part extracellular ions. However, unlike the determination of plasma chloride, the determination of serum sodium is a

difficult and time consuming task. The use of the flame spectrophotometer has made sodium determinations available in most large hospitals but there remains a large number of institutions that are not so fortunate and another method to solve the problem must be sought. Since the total anions must equal the total cations in the extracellular fluid an indirect and fairly accurate method of arriving at sodium concentration in the plasma is possible without direct determination of serum sodium.

Reference to a diagram of the plasma modified from Gamble[3] gives a good mental picture of its electrolyte distribution.




It can be seen in the diagram that potassium plus calcium plus magnesium equals 13, and this 13 plus sodium equals the total cations. It also can be seen that phosphate plus sulfate plus organic acids and proteins equals 25 mEq/L and this 25 plus the concentration of chlorides and bicarbonate equals the total concentration of anions per liter. Therefore, it can be said that:

(d) $Cl^-$ plus $HCO_3^-$ plus 25 = $Na^+$ plus 13, or

(e) $Cl^-$ plus $HCO_3^-$ plus 12 = $Na^+$

In other words, by knowing the plasma chloride and bicarbonate *and by knowing that the other ions are in relatively normal concentration* it is possible to calculate the approximate concentration of sodium. One can be sure that if the serum calcium is disturbed more than 2 or 3 milliequivalents per liter severe and obvious symptoms will result (tetany, numbness of extremities, and carpopedal spasm). Disturbances of the serum potassium of more than 2 or 3 milliequivalents also will cause diagnostic symptoms, or may even be fatal. Magnesium concentration is apparently rarely disturbed.

The most significant aberration is due to renal insufficiency which will cause a retention of sulfates and phosphates and organic acids. If the urinary volume is satisfactory and if the kidneys have manifested the ability to concentrate (as determined by the urine specific gravity) one can be fairly sure that a significant increase in the serum concentrations of sulfates and phosphates does not exist. A ketosis will, of course, elevate the organic acid concentration in the plasma. This elevation is frequently significant in diabetic acidosis. Absence of acetone bodies in the urine is fairly good assurance that no elevation of organic acids is present in the plasma. The mild acetonuria of carbohydrate starvation which disappears after treatment with 1 or 2 liters of glucose solution probably does not reflect a significant change in serum organic acids. The milliequivalent value of plasma proteins will not usually be disturbed more than a few milliequivalents per liter. Thus, we see that after an adequate physical examination and a urinalysis one can usually determine whether it will be safe to use this mathematical dodge to estimate plasma sodium concentration. The plasma carbon dioxide power as done by the bedside method will represent approximately plasma bicarbonate (in milliequivalents per liter).

Once the plasma sodium has been calculated or determined, a formula similar to the one for chloride replacement can be used to determine the quantity necessary to replace the deficit:

$$\text{(f)}\quad \frac{\text{Body Wt. in Kg.}}{5} \times (142 \text{ minus patient's } Na^+/L) \text{ plus } \frac{\text{Liters } H_2O \text{ retained}}{3} \times 142 = \text{sodium needed for repair to normal hydration (mEq.).}$$

When the quantity of sodium needed to repair the deficit is determined the quantity necessary to replace loss during the repair period must be determined also and given.

Average figures for calculating sodium loss are:

| | |
|---|---|
| Gastric suction | 60 mEq/Liter |
| Small bowel suction | 100 mEq/Liter |
| Bile (fistula) | 150 mEq/Liter |

Again, as in replacing water and chloride deficit, the original estimate of sodium deficit can be modified as losses manifest themselves in the form of drainages.

To return to our example of the man weighing 50 Kg. with intestinal obstruction for whom we have already calculated water and chloride requirements, he was computed to have a plasma sodium of 133 mEq/L as follows: The plasma

carbon dioxide combining power determined at the bedside with plasma chloride at the time of admission was 39 mEq/L. Returning to our formula

(e) $$Cl^- \text{ plus } HCO_3^- \text{ plus } 12 = Na\dagger$$
$$83 \text{ plus } 39 \text{ plus } 12 = 133$$

Knowing that the kidney function was normal and that there were no acetone bodies in the urine, we could use the formula:

(f) $$\frac{\text{Body Wt. in Kg.}}{5} \times 142 \text{ minus patient's } Na^+/L \text{ plus } \frac{\text{Liters } H_2O \text{ retained}}{3} \times 142$$

or $$\frac{50}{5} \times (142 \text{ minus } 133) \text{ plus } \frac{3.0}{3} \times 142$$

or $$(10 \times 9) \text{ plus } (1.0 \times 142)$$

or $$90 \text{ plus } 142 = 232 \text{ mEq. of sodium necessary to repair deficit.}$$

To complete the example: The patient lost 1,500 cc. by gastric suction which contains 60 mEq/liter. Thus, 1.5 × 60 equals 90 mEq. of sodium to replace that lost through gastric suction. Thus, 232 plus 90 equals 322 mEq. of sodium necessary to give the patient during the repair period.

### POTASSIUM

Since an overdose of potassium is a serious mistake and since hypokalemic states can be corrected slowly as a rule without disaster, the use of large doses of potassium intravenously is discouraged until the situation can be appraised. In the treatment of dehydrated and depleted patients potassium should not be given in the initial 1,000 cc. of fluid intravenously, but should be withheld until adequate urinary flow is confirmed (40 to 50 cc. per hour). When adequate urinary output is present, 40 mEq. of potassium should be given for each day that the patient has been vomiting or has been unable to eat. Also, he should be given an additional 40 mEq. per 24 hours during the repair period, and an additional 15 mEq. for each liter of vomitus, gastric suction, and small bowel suction, during the repair period.

Serum potassium determinations, like sodium determinations, are difficult and sometimes not available. However, they are very important in pointing the way for further treatment. *Since potassium is for the most part an intracellular ion no attempt should be made to calculate potassium needs quantitatively from the serum level. The EKG may be the laboratory aid that gives the first tip in case of hypokalemia.*

To return to the man weighing 50 Kg. who had been sick two days before his admission to the hospital. Since he had no oral intake during that period we will give him 80 mEq. of potassium (2 days × 40 mEq.) to replace his deficit. In addition, we will give 40 mEq. for the day of the repair period; and since he lost 1,500 cc. of gastric contents via nasogastric suction an additional 22 mEq. (1.5

times 15) is needed. Thus, 80 plus 40 plus 22 equals 142 mEq. of potassium to be given during the repair period.

In the light of all these considerations our actual treatment of this man weighing 50 Kg. who needs 5,750 cc. of water, 398 mEq. of chloride, 322 mEq. of sodium, and 142 mEq. of potassium evolved itself as follows, using standard available solutions:

500 cc.—5% glucose in distilled water.
1,000 cc.—5% glucose in 0.9% NaCl with 20 mEq. of KCl and 500 mg. of ascorbic acid added.
1,000 cc.—5% glucose in distilled water with 30 mEq. KCl and 500 mg. of ascorbic acid and 2 cc. Betalin added.
1,000 cc.—5% glucose in 0.9% NaCl with 20 mEq. KCl and 500 mg. of ascorbic acid added.
1,000 cc.—5% glucose in distilled water with 20 mEq. of KCl and 500 mg. of ascorbic acid and 2 cc. Betalin added.
1,000 cc.—5% glucose in distilled water with 30 mEq. of KCl and 500 mg. of ascorbic acid and 2 cc. Betalin added.

This will furnish:

5,500 cc. —water
310 mEq.—sodium (155 in each liter of 0.9% NaCl)
120 mEq.—potassium
430 mEq.—chloride (since potassium was added as potassium chloride—NaCl plus KCl = 430)

These figures do not correspond exactly to the estimated needs. However, they represent a rounding off of the figures to conform to available solutions. *This is probably as accurate as are the calculations used to determine the fluid and electrotype needs.* Currently we are mixing our own solutions to achieve greater accuracy and flexibility. We recognize that the computations can only approximate the actual needs, but they do give a reasonably sound starting point in the treatment of the specific fluid and electrolyte disturbance. The rate at which these solutions should be given; the reason for the sequence of administration as listed; and methods for observing the patient's tolerance to the massive infusion will now be discussed.

## SPECIFIC STEPS IN THE MANAGEMENT OF DEHYDRATED AND DEPLETED PATIENTS

In order to carry out the *repair* program a definite plan of attack is useful. The decision on a definite period for the *repair period* has already been mentioned. After evaluating the history and physical examination a 17 or 18 gauge needle should be inserted in an accessible vein. With this initial venipuncture blood should be withdrawn for plasma chlorides, carbon dioxide combining power, and hematocrit. Leaving the needle in the vein, the syringe is removed and a three-way stopcock is attached through which 1,000 ml. of 5 per cent glucose in distilled water is started. Then the arm should be secured well to an armboard and a water manometer attached to the three-way stopcock and the venous pressure taken.

With this set-up the venous pressure can be determined very easily by turning the stopcock so that the glucose solution fills the manometer and then turning it so that the glucose in the manometer runs into the vein, the level in the manometer where the glucose solution stops falling, expressed in centimeters above the level of the angle of Lewis of the sternum, is the venous pressure in cm. of water. This should be done three times and the average of the three taken as the final reading. At this point the relationship of the level of the arm to the angle of Lewis of the sternum should be noted so that the relationship can be duplicated for subsequent venous pressure determinations.

The patient's urinary bladder should then be catheterized and a retention catheter inserted. The catheter should be connected to a calibrated bottle for constant drainage so the nurse can record hourly urinary output. If intestinal intubation and suction is to be used the contents should be collected in a calibrated bottle to make frequent measurements of output possible. Complete urinalysis should be done on the initial specimen and then a specimen should be collected hourly directly from the catheter and a specific gravity determination made.

Within half an hour after starting the first liter of water intravenously it will be possible to compute the quantities of water, chlorides, sodium and potassium to be given in the repair period. Once the total quantity of fluids to be given in a definite number of hours has been decided upon the rate of flow can be regulated. Most fluid administration sets deliver 15 drops to the cc. Therefore, drops per minute times 4 equals the number of cc. per hour. In other words, if the set is delivering 15 drops per minute, this would be one cc. per minute, or 60 cc. per hour. Thus, the practical mental calculation is possible (15 times 4 equals 60). Conversely, the number of cc. per hour divided by 4 equals drops per minute. Therefore, if it was calculated that a patient should receive 5,750 cc. of intravenous fluids in a 12 hour period, the calculations should be as follows:

5,750 divided by 12 hours equals 480 cc. per hour and 480 cc. per hour divided by 4 equals 120 drops per minute.

Thus, the fluids could be regulated to drop 120 drops per minute and the total quantity of fluids would be given to the patient in the prescribed 12 hours.

After the total water, chloride, and sodium and potassium requirements of the patient have been estimated by the previously described calculations the second liter of fluid given can contain a part of these ions.

The importance of the initial urinalysis has already been discussed. The nurse's record should show the quantity of urine excreted in each hour. This should be correlated with the specific gravity of each of the hourly specimens. Once the urinary hourly volume has exceeded 50 cc. per hour and maintained there for two hours the hematocrit should be repeated and compared to the initial hematocrit. This will indicate also whether hydration is being accomplished. If the fall in the hematocrit on the second determination brings it lower than 40 per cent then at that point the patient should be given whole blood (amount depending upon the hematocrit and his general condition).

The initial venous pressure, mentioned earlier, is of most importance when it is compared with subsequent pressure readings. These can be done as frequently

as the patient's condition indicates. At the same time that the venous pressure is taken the patient's lungs should be examined for evidence of rales developing in the bases. Both the venous pressure and a statement about the presence or absence of rales should be recorded in the chart every time the observations is made. In a patient in whom cardiac disease is suspected these observations should be made after the administration of every liter of fluid. Also, in the adult patient with no evidence of cardiac disease, who is receiving fluids at the rate of 500 cc. or more per hour, these observations should be made between every liter. In patients receiving fluids at a rate of less than 500 cc. per hour these observations can usually safely be made every four to six hours. A rise in the venous pressure of 25 mm. (or 2.5 cm.) of water is an indication to slow the rate of infusion or even stop the infusion until the pressure has returned to normal (depending upon the severity of the rise). The appearance of rales in the lungs is a similar indication to slow or stop the infusion.

As the treatment of the patient progresses the blood chemistries should be repeated at frequent intervals (from 8 to 24 hours), using the bedside testing set, depending upon the severity of the depletion that is being treated and how rapidly it is being treated.

The sequence in which the various types of fluids is given is of some importance. If the fluids that are to be given after the electrolyte needs have been determined are both fluids containing electrolytes and fluids containing only glucose in water it is a good plan to alternate the liters so that the patient gets a liter of electrolyte containing fluid followed by a liter containing only water and glucose.

Obviously no two patients can be treated alike when large quantities of fluids are being replaced rapidly. Also, the physician can lead the patient into serious trouble if massive replacement therapy is undertaken without very close, alert, and careful observation. The foregoing discussion only outlines a regime that we have found useful to more or less force us to watch our patients by requiring frequent observations both by physical signs and laboratory determinations.

## DISCUSSION

The plan of attack that we have outlined for the treatment of acute dehydration is, of course, subject to variation and improvision. We frequently have occasion to seek help from the clinical laboratory, and do not wish to imply that the *bedside methods* are the only source of laboratory results available to us. However, we do use the *bedside laboratory* extensively and have controlled the treatment of many patients with it alone. Its many advantages are obvious. So frequently these patients are admitted during the night hours and the house officer treating the patient is able to complete his *work-up* of the patient, using the *bedside* laboratory methods, and start treatment in less time than is necessary to alert the clinical laboratory personnel. Also, we occasionally repeat various laboratory determinations at frequent intervals, a use for which our *bedside* kit is admirably suited. The need to request a non-protein nitrogen determination from the clinical laboratory has already been discussed, and we frequently order this test if our urinalysis indicates it. Also, the shortcomings of the method of cal-

culating serum sodium concentration that we have presented are obvious. Therefore, we sometimes have occasion to request a serum sodium determination, and also a serum potassium determination. However, the cases that indicate these determinations (like those indicating non-protein nitrogen and other determinations) are usually complicated by the presence of renal disease. We do believe, however, that the vast majority of patients with dehydration and/or electrolyte deficiency can be diagnosed and treated adequately using only the *bedside* methods.

The example case cited may seem to have received a very large quantity of fluids intravenously over a short period of time. However, he did not have extreme diuresis or suffer any dangerous effects from this vigorous hydration. *Too much warning cannot be given concerning the dangers of overhydration or too rapid hydration.* This is why we believe that our plan of close, careful observation of the urinary volume; frequent auscultation of the lungs; and frequent venous pressure determinations is a crucial safeguard in treating these patients.

We recognize the shortcomings of the formulas presented for calculation of electrolyte needs. However, they serve a very useful function for us in training the house staff to think in the proper direction. If some sort of mental gymnastics is not indulged in while planning the therapy for these patients the tendency in prescribing fluids will be to *give them two bottles of saline and one of water* or some other such unthinking regime. A physician's trend to be too precise in his mathematical evaluation of electrolyte needs is as undesirable as to be too empirical in his therapy. He who accepts fluid balance as a mathematically precise science and dogmatically applies all the formulas, rules, and average figures, is as surely doomed to encounter disastrous results as is he who blindly gives a favorite number of bottles. The maintenance of a sick patient on parenteral therapy alone is as much an art as it is a science. The laboratory results *must* be considered in the light of the patient's clinical appearance, and calculation of *deficit* or *excess* of water and electrolytes must be tempered with good clinical judgment.

## SUMMARY

A *bedside method* of making plasma and urinary chloride and plasma carbon dioxide combining power determinations has been presented.

A plan of treatment of the acutely dehydrated patient, utilizing good clinical evaluation together with *bedside laboratory methods*, has been described.

These laboratory methods and the plan of management of acute dehydration present have been used successfully in our hospital by the house staff.

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# ESTROGEN THERAPY IN THE MANAGEMENT OF ADVANCED BREAST CANCER*

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Cancer of the female breast is one of the most frequently occurring of the malignant neoplasms in human beings, but at the same time, it is often one of the most unpredictable and bizarre in its behavior. Certainly the regression of actively growing deposits of breast cancer in elderly women in response to the administration of estrogenically active compounds stands as one of the truly baffling medical puzzles of the day. Since the first description of this phenomenon about 10 years ago[2, 3, 6] many papers have been published describing the details of the therapeutic responses obtained as well as of results of inquiries into the mechanism of action of this group of compounds, but as yet no satisfactory rationale for this therapeutic regimen has been forthcoming. An excellent review of the literature has been presented recently by Nathanson and Kelly.[11] The purpose of this presentation will be to attempt to delineate the role that estrogenic hormones should play in the everyday palliative treatment of advanced breast cancer in older women.

## CLINICAL OBSERVATIONS

One hundred patients treated through the University of Minnesota Hospitals Tumor Clinic between March 1946 and May 1952, whose course we were able to follow, and who had lesions so located as to permit relatively accurate clinical evaluation are included in this study. None of the patients had had significant previous hormone therapy for their breast cancer with the exception of a few patients who were surgically or roentgenologically castrated at the time of their mastectomy. Eight patients are included who received therapy for less than six weeks, treatment being terminated by their deaths. Excluded from consideration are 9 patients who did not return to the clinic and whose course of treatment and response, therefore, could not be followed. Information received indicated that most of these women discontinued medication after a week or so because of nausea. All patients treated were past the menopause and had either inoperable primary disease or recurrent and/or metastatic lesions usually rather widely distributed. Ninety-five patients were more than five years past their menopause,

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and their response to treatment makes up the major portion of this report. Sixty-five received diethylstilbestrol orally, 15 mg. daily, while 30 received ethinyl estradiol 3 mg. per day by mouth. The response of 5 patients less than five years past the menopause will be considered only briefly; 3 received stilbestrol and 2 ethinyl estradiol.[1]

In all but 2 cases, where the superficial tissues of the body were involved, histologic proof of the nature of the disease was obtained prior to the institution of therapy. In cases where the lungs and/or skeleton were the only tissues involved we were dependent upon roentgenographic examination to establish the diagnosis.[2] In a majority of the cases roentgenographic survey, including films of the chest, skull, lumbar spine and pelvis and other portions of the skeleton as indicated, was obtained prior to the institution of therapy in order to assess the extent of the disease process as accurately as clinically feasible. Such roentgenographic studies were usually repeated at intervals after the institution of therapy as the course of the patients' disease dictated. It is obvious that with our present technics the accurate evaluation of the majority of intra-abdominal lesions is impossible. Unfortunately for the completeness of this study, most patients who died could not have an autopsy since they died either at home or in a hospital in their local community.

The distribution of lesions in this group of patients should not be taken as a true representation of the distribution of recurrent or metastatic breast cancer in patients of this age groups since, as experience was accumulated with this type of therapy, more patients with relatively localized disease involving the soft tissues of the body were included and fewer patients with lesions of the bony skeleton were selected because of the poor response obtained with such lesions. In considering the response of patients in general, if lesions involving the soft tissues of the body regressed significantly, the patient was classified as having shown a favorable response whether or not lesions of the bony skeleton responded in a similar fashion. However, only those patients in whom all of the soft tissue lesions decreased significantly in size for a period of three months or more were considered as having responded favorably. Those persons in whom the soft tissue disease remained unchanged, or in whom the initial measurable decrease in the size of the tumor deposits was maintained for less than three months, were classified as nonresponders. According to this classification 42 (44 per cent) of the patients who were five or more years past their menopause showed a favorable response to estrogen therapy. It is of interest to note that the age of the patient did not effect either her chance of responding favorably nor the excellence of the response obtained as long as she was five or more years past either a natural or an artificially induced menopause.

Regression of metastatic and/or recurrent deposits of breast cancer occurred more frequently when the superficial soft tissues of the body were involved than when other tissues of the body were afflicted. Of 40 patients who had metastatic or recurrent disease involving the skin, subcutaneous tissues or superficial lymph nodes following the surgical removal of their primary disease, 22 (55 per cent) showed definite regression. In 16 of these the regressions were clinically complete

while in the other 6 a definite measurable decrease in the size of all the tumor masses occurred.

Somewhat poorer results were obtained in patients with extensive, previously untreated, carcinoma. Of 27 such patients, only 7 (26 per cent) showed major regressive changes, and in none of these was a clinically complete regression of the primary lesion obtained. Only 6 of this group of patients were deemed inoperable solely because of the extent of their primary lesion; the rest had metastatic lesions as well, which in most instances were widely distributed. Many of these patients were in poor general physical condition at the beginning of therapy. One patient deserves special comment because, as her primary inflammatory carcinoma regressed after the institution of therapy, she developed numerous nodal metastases throughout the cervical region and, therefore, was classified as a *nonresponder*. This is the only example we have seen in which some lesions involving the superficial soft tissues regressed in response to estrogen while at the same time new soft tissue lesions appeared elsewhere. In addition 4 patients not operated upon were seen with massive reactivation of the disease several months after a course of roentgen ray therapy. Of these, 2 showed a very satisfactory response to estrogen therapy.

Since in a large proportion of cases of metastatic breast cancer involving lung and/or pleura roentgen ray therapy is not indicated, the results obtained with hormone therapy in such cases is of particular interest. Of 34 patients with either pulmonary or pleural disease, 11 (32 per cent) showed a major regression of their lesions. In 7 instances the palliation was very gratifying, since the patients were moderately to severely dyspneic due to widespread parenchymal disease when first seen. Their respiratory symptomatology cleared completely, or almost completely, and this improvement persisted for from 7 to 19 months. It is interesting to note that 20 patients in this group with lung involvement also had involvement of the superficial soft tissues of the body. Of these, 6 showed regressive changes in both the superficial and the lung lesions while in the other 14 no response was noted of either group of lesions. Thus, we saw no example of a patient whose lung lesions responded differently than did her superficial soft tissue disease.

The evaluation of the response to therapy of metastatic cancer in bone is made difficult by virtue of the fact that not only must the tumor tissues decrease in size as a result of treatment, but also the bone must repair itself before roentgenographic evidence of improvement becomes visible. Of 30 patients with roentgenographic evidence of metastatic disease in the bony skeleton, repair of the lesions was seen in only 2. Both of these had large lytic lesions that calcified and became very sclerotic as treatment continued, and this repair was associated with a complete relief of pain. In 4 other cases there was suggestive evidence that at least a regression of the tumor had occurred, but no definite radiologic evidence of bone repair followed. Two of these patients had predominately blastic lesions that were shown to be progressing prior to the institution of therapy, but which remained stationary in size for 11 and 40 months under the influence of estrogen therapy while the other 2 presented lytic lesions that did not progress during 21 and 55 months of treatment. In addition to the low per cent of favorable re-

sponses seen in this group of patients with bony metastases, one woman 65 years of age with but two small lytic lesions demonstrable at the beginning of therapy experienced a most dramatic acceleration of her disease which was associatiated with the development of hypercalcemia shortly after the initiation of estrogen therapy.

Of the group of patients with lesions involving the bony skeleton at the beginning of hormone treatment, 25 had concomitant lesions of the soft tissues of the body. Ten of these showed major regressions of their soft tissue lesions, but in 6 of these 10 the lesions of the bony skeleton continued to progress even as the soft tissue lesions were resolving. Moreover, of the patients who had no demonstrable bone lesions at the beginning of therapy and in whom soft tissue disease regressed satisfactorily under the influence of estrogen therapy, 3 developed progressive bone lesions while the soft tissue lesions remained quiescent. These observations emphasize the fact that metastatic deposits situated in bone respond much less often to estrogen therapy than do those in the soft tissues of the body even when the metastatic deposits in the different sites originally came from the same primary tumor.

Although the accurate appraisal of most intra-abdominal lesions is impossible, 6 patients had clinically demonstrable intra-abdominal disease at the institution of therapy. Three of these had large masses palpable per vagina and 1 had a massively enlarged liver associated with ascitic fluid containing tumor cells. None of these lesions regressed with therapy. Two patients with intra-abdominal disease, however, did show striking improvement. One presented with a complete obstruction of the large bowel secondary to metastatic tumor and required a colostomy to control her immediate symptomatology. With estrogen therapy she gradually began to pass feces per rectum and the colostomy partially closed. This improvement, associated with a complete disappearance of many cutaneous metastases, continued for 27 months before the obstruction recurred. The second patient had a massive, diffuse involvement of her entire mesentery by metastatic tumor proved at laparotomy prior to the beginning of hormone therapy. Her severe constipation gradually disappeared with treatment, and a re-exploration after five months of therapy, failed to reveal either gross or microscopic evidence of tumor. This patient lived without symptoms or signs of recurrent disease for 14 months before she died suddenly with symptoms suggesting a dissecting aneurysm (no autopsy could be obtained). It is evident, therefore, that intra-abdominal metastatic disease can be favorably effected by estrogen therapy, but how frequently this occurs is impossible to determine.

Two other patients deserve brief mention. One presented following the rapid onset of almost total blindness in the left eye two years after a metastatic lesion had been surgically removed from her left cerebral hemisphere. With estrogen therapy her eyesight gradually returned; the severe optic nerve atrophy disappeared; and she remained well for more than 20 months. Because she felt so well she discontinued her therapy and within four months developed a massive recurrence of disease in the right side of her neck which again responded favorably to estrogen therapy. The second patient had severe radicular pain which at laminec-

tomy was found to be caused by extensive involvement of the spinal meninges with metastatic breast cancer. Within two months after beginning estrogen therapy the pain had disappeared completely as had two axillary nodes that had been shown to contain tumor by aspiration biopsy. This patient has remained symptom free without clinical evidence of metastatic disease for the 28 months that she has been followed.

As mentioned before, only 5 patients less than five years past their menopause were treated. All of these had metastatic disease involving the superficial soft tissues of the body, but only 1 showed significant regression. On the other hand, 2 of these 5 patients experienced what appeared to be an alarming acceleration in the growth of their disease following the institution of treatment. In 1 of these 2 patients the disease stopped its very rapid progression when estrogen was discontinued.

In order to assess the value of estrogen therapy in advanced breast cancer, we need to know much more than the per cent of patients showing an initial favorable response. The question of primary importance is: *Does estrogen therapy prolong the useful life of those who show a favorable initial response and, if so, for how long?*. Unfortunately, it is impossible to answer this question satisfactorily since, to my knowledge, there has been no series published in which the survival of a large number of patients has been determined using the appearance of metastatic disease as the point of reference. At present the best we can do is to determine the duration of the regression obtained by estrogen therapy. This certainly does not give us an accurate estimation of improvement since all lesions may not reactivate simultaneously. As an example, 1 of our patients had numerous subcutaneous nodules at the time of initiation of therapy. Her main complaint, however, was moderately severe dyspnea due to widespread infiltrative metastases in both lungs. On estrogen therapy both subcutaneous and pulmonary lesions regressed completely with the complete disappearance of respiratory symptoms. The subcutaneous lesions began to reappear after 6 months while there was no evidence of returning pulmonary disease until 13 months later. Furthermore, using the length of the initial response as an index of the period of palliation can be somewhat misleading because many patients whose disease reactivates while they are still receiving the hormone will show a second significant regression of lesions when estrogen is discontinued. In our series we had 14 patients who responded favorably to the initial therapy and who continued on their medication up to the time that reactivation of their disease occurred. With the discontinuance of the hormone as the only form of treatment 9 of these patients exhibited a second definite regression of their lesions lasting from 6 weeks to 9 months.

However, in order to get some idea of the duration of the effect of estrogen therapy, we have measured the average length of the initial response in those cases whose disease involved the soft tissues of the body using as the *duration of response* the period from the institution of therapy to the first sign of reactivated growth of tumor in any of the soft tissues. These data are given graphically in figure 1, as are the survival curves for both the *responders* and the *nonresponders* who had soft tissue involvement. The duration of these favorable responses ranged from 3.5 to 84 months (the regression still continues in this latter instance)

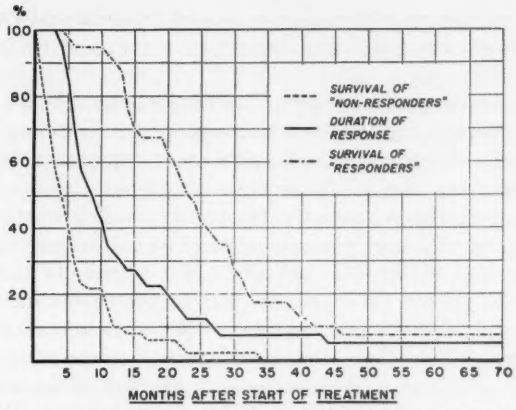


FIG. 1. Graphic presentation of the duration of initial response of soft tissue lesions in 40 patients five and more years past the menopause treated with estrogen, and the survival curve for these patients. The survival curve for 49 *nonresponders* of similar age with soft tissue lesions is also shown.

with an average of 15 months. The average survival time of these patients from the institution of therapy was 29 months with 3 patients still living free of symptoms and free of gross evidence of disease at 28, 72 and 84 months. It is evident from these data that in many of the patients who responded favorably to treatment the disease was controlled for significant periods of time and that even after the first evidence of a regrowth of the cancer had appeared the patients lived, often relatively free of symptoms, for many months more. In fact, it often appeared as if the tumors tended to grow more slowly after reactivation than they had prior to therapy. In contrast, the average survival of the patients with soft tissue disease that did not show an initial favorable response was only 6.7 months. It is certainly not justified, however, to conclude that the difference in these two survival times represents the contribution of estrogen therapy for more of the *nonresponders* had massive disease at the time treatment was initiated. Furthermore, there is no way of knowing whether or not patients with inherently slow growing cancer respond to estrogen therapy more frequently than do those with rapidly progressing disease.

To most people the mere prolongation of life is an hollow accomplishment unless the added days are useful to the patient and are relatively free of pain. It should be emphasized that, in general, these patients were comfortable and going about their usual daily activities as long as their disease remained *controlled* by hormone administration. Usually many months elapsed after reactivation became evident before the patients were bedridden.

## PLACE OF ESTROGEN THERAPY IN THE PALLIATIVE MANAGEMENT OF ADVANCED BREAST CANCER

Although in many instances remarkable results can be obtained by the use of estrogen therapy, it is evident that this type of treatment must not be used in cases where curative procedures are applicable. At the present time it would also

seem wisest to limit the use of estrogenic hormones in the currently recommended doses to patients who are five or more years past a natural or an induced menopause.

Since a characteristic of breast cancer is to metastasize widely, it is a frequent experience to have new soft tissue lesions appear almost before roentgen ray therapy to the initial area of involvement has been completed. The generalized response of soft tissue lesions obtained with estrogen therapy is, therefore, greatly to be desired. For this reason it has been our policy to place all patients in this age group who have soft tissue metastases and/or recurrences on estrogen therapy unless there are specific contraindications. Patients are then seen at weekly or bi-weekly intervals during the first two to three months of therapy during which time careful measurements of all lesions are made. Therapy is continued as long as the lesions remain stationary or decrease in size. However, as soon as definite evidence of an increase in the size of the lesions appears, estrogen therapy is abandoned in favor of irradiation whenever this is feasible. Unfortunately in a number of patients a measurable decrease in the size of the tumor deposits during the first two to four weeks of treatment with estrogens will be followed immediately by resumption of tumor growth. On the other hand tumor regression may not be evident until after three to four months of continued therapy, but in our experience in such late *regressions* the tumor deposits have remained stationary in size from the onset of therapy. In our material there is not a good correlation between either the rapidity of appearance or the completeness obtained in the initial regression and the length of time that the regression is maintained. In certain instances, rapidly occurring, clinically complete regressions have lasted but six months while in others slowly progressing and clinically incomplete regressions have been sustained for very much longer periods of time.

On the other hand, when the skeleton is involved with metastatic breast cancer, localized roentgen ray therapy has been found to be rather effective. Most clinics report calcification of lytic lesions in approximately one-third of cases with a relief of pain and a cessation of progressive bone destruction in an additional one-third of cases.[5] This is certainly far superior to the results obtained with any of the current types of hormone therapy. It is also evident that it is the metastatic deposits located in the major weight bearing areas of the skeleton that pose the greatest immediate threat to the patient's life and comfort. Therefore, our policy is to survey all patients with evidence of metastatic or inoperable primary disease to determine what, if any, bony structures are involved. When metastases are demonstrated in any major weight bearing areas of the skeleton, they are treated by roentgen ray therapy to relieve pain and to forestall, if possible, the development of pathologic fractures. When the involvement of the skeleton is widespread and/or the patient also has soft tissue metastases we direct roentgen ray therapy toward those lesions in the major weight bearing areas and then start a course of hormone therapy (estrogen therapy if the patient is five or more years past the menopause) with the hope of improving the other areas of disease. In cases where the only demonstrable metastatic disease involves a relatively localized area of the skeleton, we believe that roentgen ray treatment should be

used with hormone treatment being reserved until a time when the disease becomes clinically disseminated. Furthermore, skeletal metastases developing or progressing during a remission of soft tissue disease under the influence of estrogen are treated by roentgen ray therapy while the estrogen is continued.

How long should the administration of estrogen be continued in patients that respond favorably? It has been our policy to continue therapy, whenever possible, until the lesions again reactivate, because on several occasions we have seen patients discontinue therapy and within two to four months experience a reactivation of their disease, which usually, however, again responded to estrogen administration. Also, as pointed out earlier, patients who reactivate their soft tissue metastases while continuing on therapy very frequently show a second regression of these lesions upon discontinuance of the medication. Since these second regressions may last for several months, we never begin a new type of therapy after reactivation of disease until the response of the lesions to the discontinuance of estrogen has been evaluated. In two or three cases where this second regression had lasted for several months, a third regression of the re-reactivated lesions has been obtained by a second course of estrogen.

## GENERAL CONSEQUENCES OF ESTROGEN THERAPY

The most prominent side effects of estrogen administration are nausea and general malaise. A high per cent of the patients will experience moderate to severe nausea upon beginning treatment with these relatively large doses of estrogen, and many will complain of associated muscular aching and general malaise. If the ingestion of estrogen is continued, however, these disagreeable effects usually subside and disappear within one to two weeks. We have heard of no effective medication to combat these undesirable initial reactions, but in severe cases we have had good success in circumventing the nausea by using injectable material, diethylstilbestrol in oil 5 mg. per day intramuscularly, for a period of one to two weeks and then returning to the oral preparation usually without the return of nausea. In a few instances, however, the patients continued to complain of general malaise—and in 1 patient nervousness—to the extent that they insisted that the therapy be discontinued. Occasionally, also, a patient will continue to have annoying degrees of nausea as long as the oral medication is continued.

Since many tissues of the body normally are influenced by estrogenic hormones, it is not surprising that numerous alterations other than the changes in tumor growth may manifest themselves during a course of estrogen treatment. The most serious of these is the retention of body fluids. The exact mechanism of this fluid retention is not known, but we have found that not only is the thiocyanate space expanded with therapy, but also the cellular fluid compartment.[7] These patients are mainly in an older age group, so that the additional strain on the cardiovascular system incident to this retention of fluid may precipitate cardiac decompensation. Therefore, patients with known significant cardiac disease should be given these doses of estrogen only with the greatest of caution. Furthermore, in any patient who develops dependent edema while on therapy every

effort should be made, after thoroughly evaluating her cardiac status, to control as completely as possible the accumulation of edema fluid. The most successful method in our hands for so doing has been to institute a rigid low sodium diet attempting to limit intake to 300 mg. per day. Ammonium chloride and/or mercurial diuretics alone without a drastic reduction in sodium intake usually has been unsuccessful in combating this edema. To indicate the severity of this problem, we must report that three patients in this series died with symptoms suggesting cardiac decompensation because they failed to return to the clinic, yet continued their intake of estrogen after significant edema appeared. In addition, therapy had to be discontinued in 2 other patients because of the appearance of cardiac decompensation and our inability to control adequately the accumulation of fluid.

The other general effects of estrogenization are not as serious. Although a few patients feel less well while on therapy, many volunteer the information that they feel better generally than they have for a long time. Areolas usually become reddened early in the course of therapy and may become tender to pressure as may the entire breast. With continuation of treatment this tenderness generally disappears and the areolas become rather darkly pigmented. Nevi may also become very dark and increased pigmentation of the axillas, linea alba and perineum may be noted in certain cases. Skin turgor may improve, but occasionally patients complain of dryness and itching of the skin and an increase brittleness of the finger nails and hair. Patients may also develop a mild to moderately severe urinary incontinence which is usually experienced only in situations of physical stress, but rarely may be sufficiently severe to be extremely embarrassing to the patient. Uterine bleeding has not been a serious problem in our cases. Only 3 patients had episodes of severe bleeding while they remained on the medication, although several others reported short periods of mild spotting. Certainly this has not been nearly as great a problem as in patients when smaller doses of estrogen are used continuously to control menopausal symptoms. This difference is probably related to the dose of estrogen administered rather than to the age of the patients.[9] When significant bleeding has occurred it has been our policy to discontinue therapy for two or more weeks to induce a complete shedding of the endometrium and then to restart therapy. When the medication is discontinued in patients who have had no previous bleeding, withdrawal bleeding occurs in approximately half the patients, but usually lasts for no more than 5 to 10 days and is seldom so severe as to require intervention.

## MECHANISM OF ACTION OF ESTROGENIC HORMONES

Although several suggestions have been made as to why the administration of estrogens to postmenopausal women should cause regressive changes in established cancer of the breast, none of the explanations seems to fit all the facts as they present themselves. Haddow, and associates[1, 6] originally used estrogenically active compounds in the treatment of animal and later of human cancer on the premise that in large doses they were general growth inhibitors. However, the clinical trials showed that estrogens were effective in causing regression only in

instances of cancer of the breast, prostate and occasionally of the bladder. It has also been suggested, since the growth of normal breast tissue in animals can be inhibited by the administration of very large doses of estrogen, that in treating human breast cancer we may be using sufficiently large doses to cause a similar response in both the normal and the malignant breast epithelium. That such a situation does not, in fact, obtain has been shown in a recent study in which it was found that the normal breast epithelium of postmenopausal women usually proliferates, and sometimes remarkably so, during the course of estrogen therapy even as the neoplastic epithelium of the breast cancer is undergoing regressive changes.[8]

It would seem that any hypothesis concerning the mechanism of action of the estrogenic hormones, in causing the regression of established breast cancer, must postulate some reaction within the supporting tissues, in order to explain the regression of tumor deposits involving the soft tissues of the body at the same time that metastatic deposits, arising from the same primary tumor but involving bone, are progressing. Instances have been reported in which the stainable alkaline phosphatase within the connective tissue stroma of breast cancer deposits was found to increase during estrogen therapy.[10] It has been shown in studies of both animal and human beings that the collagenous connective tissue contains stainable quantities of this enzyme only during periods of fibroblastic activity when new connective tissue is being formed. Such a reaction was found to be very prominent in the connective tissue of normal breasts of elderly women receiving estrogen.[8] It seemed very important, therefore, to establish if fibro-

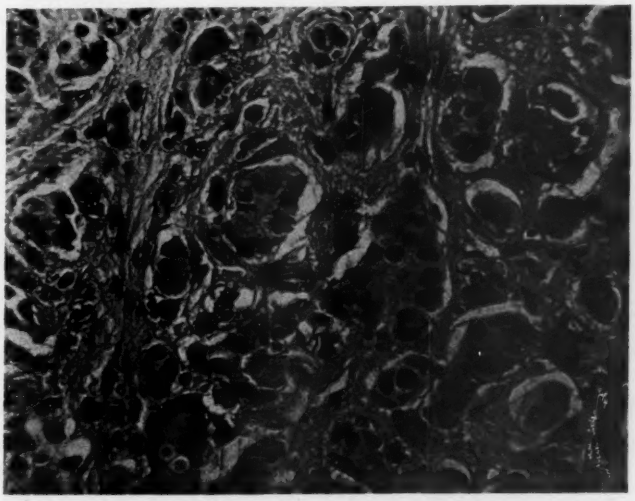

FIG. 2. A typical area of a breast cancer metastatic to the dermis of a 77 year old woman just prior to the institution of estrogen therapy. There was no histologic evidence of significant desmoplasia in this lesion, and staining for alkaline phosphatase was negative except in the capillaries. Mag. ×375.

plasia regularly occurred in the connective tissue of breast cancer deposits as they underwent regressive changes.

In 9 patients we obtained tissue for biopsies before the institution of estrogen therapy and again during the active phase of tumor regression (14 biopsies). In 4 additional patients tumors were studied after a partial regression had occurred and the tumor deposits had become stationary in size. In all instances tumors located at some distance from breast tissue were used for study so that the connective tissue proliferation present in the normal breast would not confuse the picture. The removed tissues were stained to demonstrate alkaline phosphatase as well as being prepared by special staining technics to demonstrate the detailed morphology of the collagenous connective tissue. In none of the material studied did we see any evidence, either histologic or histochemic, of fibroblastic proliferation in or about the tumor deposits as they were regressing, nor after they had partially regressed, and had become stationary in size. In fact, two of the tumors studied showed active stromal proliferation prior to therapy, but while they were decreasing in size following the institution of treatment all evidence of connective tissue proliferation disappeared. Furthermore, there did not appear to be any definite increase in the elastic fibers within the stroma during tumor regression. The microscopic appearance of one tumor is shown in figures 2, 3 and 4.

These findings would seem to be in agreement with the clinical observation that tumor deposits can disappear completely, as far as one can tell from gross examination, under the influence of estrogen and leave no area of residual scar-

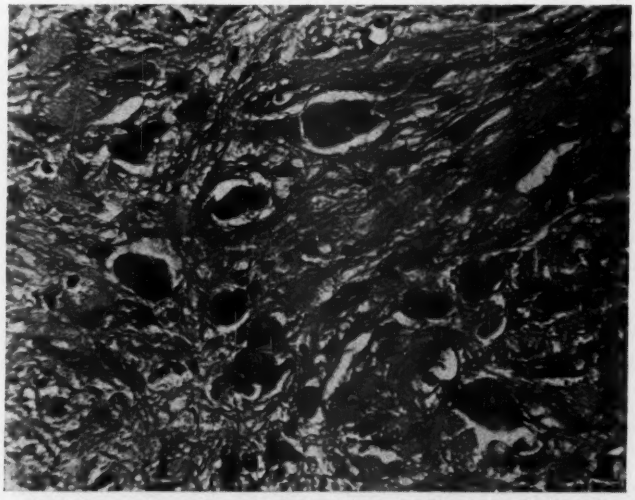

FIG. 3. A typical area from the same lesion illustrated in figure 2 after the patient had been ingesting 3 mg. of ethinyl estradiol for four weeks. The lesion had reduced considerably in thickness by the time this biopsy was made. Although the connective tissue has increased relatively in amount and now has a loose appearance, there is neither histologic nor histochemic evidence of fibroplasia, and the apparent increase as well as the loose appearance seems most likely due to the disappearance of tumor cells. There is very little reaction of any type about the tumor cells which now appear definitely altered morphologically. Mag. ×375.

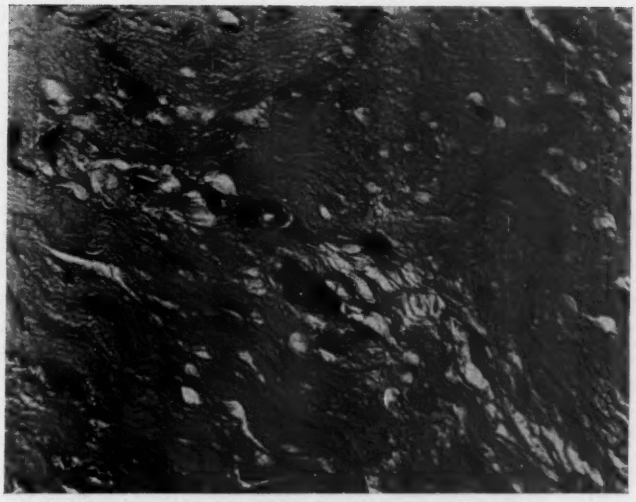

FIG. 4. An area from the same lesion illustrated in figures 2 and 3 four months after starting estrogen therapy. By this time the lesion had disappeared completely as far as one could tell by clinical examination. This small cluster of cells represents the only recognizable tumor seen in the otherwise normal appearing dermis. The connective tissue in the two biopsies made after institution of therapy was negative for stainable alkaline phosphatase except in the capillaries. Mag. ×375.

ring. A looseness of the connective tissue in the area of regressing tumors has been described[4, 12] and was frequently noted in our material, but these changes appeared to us more likely to be due to the extensive disappearance of tumor cells from the area rather than to a specific reaction of the connective tissue to the treatment. It rather surprised us that even where there was evidence of considerable degeneration of the tumor cells no active phagocytosis of tumor cell fragments was observed. On the basis of these studies we do not wish to suggest that the connective tissue stroma does not play an important causal role in the regression of metastatic deposits of breast cancer, but merely that a proliferation of the connective tissue stroma does not appear to be the mechanism by which such an effect is mediated.

It seems evident from this brief consideration that the treatment of breast cancer with estrogens may best be considered as an empirical therapy at the present time. Since, however, hormones generally do not initiate body processes, but only alter those already present, one wonders if under certain special conditions administered estrogens may not augment the hosts *natural resistance* to the progressive growth of breast cancer; however the nature of any such *natural resistance* is as yet completely unknown.

## CONCLUSIONS

Our experience with the treatment of inoperable, recurrent and metastatic breast cancer in elderly women with estrogenic hormones has been reviewed. On

the basis of this experience and the experience of others, certain conclusions concerning the role of this type of treatment in the palliative management of this disease have been reached.

We believe estrogen therapy in women five years or more past the menopause to be the treatment of choice where the soft tissues of the body are involved with the neoplastic process, with roentgen ray therapy being used where possible in those cases that do not respond to this type of hormone treatment.

Although a small percent of cases with bone involvement will show a favorable response, we believe that roentgen ray therapy should be directed to all lesions in bone when they are relatively localized or when they involve major weight bearing areas even though the disease is widely distributed and all areas of involvement cannot be included in the field of treatment. In the latter situation estrogen therapy may be combined with roentgen ray therapy in an attempt to obtain generalized improvement particularly where soft tissues are also involved.

Our experience would indicate that although estrogen therapy is not curative, very significant and oft-times prolonged control of the disease can be effected by its use. As far as we can judge at the present time, the only rationale for the use of this seemingly paradoxical therapeutic regimen lies in the clinical demonstration of its effectiveness.

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# AN EVALUATION OF ARTERIAL LIGATION IN PORTAL HYPERTENSION

## A CLINICOPATHOLOGIC STUDY WITH CASE PRESENTATIONS

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"The moment of tying the ligature
is, indeed, a dramatic one".
William Stewart Halsted (1912)

Cirrhosis of the liver with its portal hypertension and its complications of exsanguinating hemorrhage from esophageal varices and debilitating ascites is still a therapeutic challenge to the medical profession. Although great strides have been made in the palliative alleviation of these dreadful complications, and a large number of ingenious methods have been advocated, these have all proved unsuccessful in the treatment of the majority of patients afflicted with this disease. The older procedures, such as omentopexy of Talma-Morison, esophagoscopic injection of sclerosing solutions into the varices, splenic artery ligation (Everson and Cole[10]) with or without splenectomy, and ligation of the left gastric and the right and left gastro-epiploic arteries, as suggested by Flerow,[12] have seen their day and have fallen by the wayside. More recently Phemister and Humphreys[25] have resorted to esophagogastric resection, and Som and Garlock[29] recommended gauze packing about the esophagus through a mediastinotomy. The work of Whipple,[30] and of Blakemore and Lord[6] on portacaval and splenorenal shunt procedures as a decompressing mechanism for portal hypertension has become a valuable procedure in the interim control of hemorrhage from esophageal varices, but its complexity and technical difficulties have proved too great for the poor risk patient or in patients during an acute bleeding episode.

We are now passing through a new phase in the approach to this perplexing problem. The work of Rienhoff[26, 27] and of Berman[1, 2, 3, 4, 5] on hepatic artery ligation, with their encouraging results have been a stimulus to additional investigative work and is being evaluated by many centers throughout the country. The general attitude toward hepatic artery ligation when it was first proposed by Rienhoff was one of marked skepticism. Surgeons were only too familiar with the usual rapid, and not too dramatic, death of patients following accidental hepatic artery ligation in the course of surgery on the biliary tract. Since 1905 the experimental literature has carried such statements as the following: (a) hepatic artery ligation was almost always fatal; (b) ligation of the hepatic artery in dogs was usually fatal within 24 hours; and (c) diminution in arterial blood supply to an already hypoxic organ is an *unphysiologic procedure*. Gradually, and fortunately, this skepticism is fading away; and, with the advent of antibiotic therapy

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TABLE I

| Case | | | History of Alcoholism | Anemia | Jaundice | Hemorrhage | Ascites | Spider nevi | Palpable | | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Age | Sex | | | | | | | Liver | Spleen | |
| DK | 43 | Female | ++++ | ++++ | ++ | +++ | ++++ | + | ++++ | ++ | Died |
| LG | 57 | Male | + | + | 0 | 0 | +++ | 0 | + | 0 | Died |
| JB | 68 | Male | ++++ | + | 0 | 0 | ++++ | 0 | ++++ | ++ | Improved |
| AH | 60 | Male | ++++ | ++++ | 0 | ++++ | ++++ | 0 | 0 | + | Improved |
| TD | 62 | Male | +++ | 0 | 0 | 0 | ++++ | 0 | +++ | + | Improved |

through the work of Markowitz, Rappaport, and Scott,[21] and its value in the prevention of liver necrosis following hepatic artery ligation, the rationale for this procedure has been more thoroughly evaluated. Only time will determine the over-all statistical value of this approach for portal decompression and its place in the armamentarium of the surgeon for the treatment of Laennec's cirrhosis.

## CLINICAL MATERIAL

During the period of 1951 to 1952 we have had the opportunity to do arterial ligations in five instances. The procedure consisted of concomitant ligation of the hepatic, splenic, and left gastric arteries in 3 patients; and ligation of the hepatic and splenic arteries in the remaining 2 patients. In all instances the ligation of the hepatic artery was done proximal to the gastroduodenal branch, as advocated by Berman. Although Rienhoff emphasizes the importance of a ligation distal to this branch, we believe that this technic is more difficult, and doubt whether or not it is any more efficacious.

A clinical analysis of our cases is presented in table I.

It will be noted that 4 patients were male and one was female. Four patients admitted excessive alcoholic consumption over a period ranging from 10 to 34 years; while the fifth patient indulged in moderate alcoholism. The incidence of secondary anemia was marked in 2 patients, mild in 2, and absent in 1. Jaundice was present in a single instance at the time of operation. Two patients experienced preoperatively, massive gastrointestinal hemorrhages, which responded adequately to conservative therapy. Each patient exhibited marked debilitation from intractible ascites. The ascites necessitated frequent paracenteses averaging every two to four weeks with the removal of ascitic fluid ranging from 5–14,000 cc. Rapid reformation of ascitic fluid occurred, and this intractible ascites was the prime indication for surgery in each patient.

The mortality rate of 40 per cent for our series compares favorably with the over-all mortality of 30.4 per cent expressed by Rienhoff in a series of 23 patients. Although this rate may seem exceedingly high, we must consider the fact that 1 patient was a poor candidate from the standpoint of both surgical risk and criteria for operability. She was deeply jaundiced with marked debilitating ascites and exhibited laboratory evidences of severe hepatic damage: she died four

months postoperatively from progressive hepatorenal failure. The second death occurred in a patient who preoperatively was known to have esophageal varices as demonstrated by roentgenogram, and was operated upon for intractable ascites. Following the operative procedure he developed a massive gastrointestinal hemorrhage and, failing to respond to conservative therapy died four weeks later.

From this series of cases we have been able to draw a number of conclusions. It is the purpose of this paper to present our experiences with arterial ligation in portal hypertension, with an abstract of each case including the average preoperative and postoperative laboratory data, and a review of the experimental and clinical literature that has contributed to the establishment of this procedure. This material will be presented under the following headings: (a) hepatic necrosis; (b) esophageal varices; and (c) intractable ascites.

## HEPATIC NECROSIS

We have heard the hue and cry which had been raised that the procedure of arterial ligation in portal hypertension was without physiologic basis, and would be followed by inevitable *fetor hepaticus fatalis*. We have only to turn to the experimental literature to find abundant evidence to support this hypothesis. Haberer[17] initially demonstrated that ligation of the hepatic artery was almost uniformly fatal. Fraser[13] later showed that massive hepatic arterial ligation in normal dogs resulted in a 65 per cent mortality rate despite penicillin therapy. This figure corresponds closely with that of Laufman and co-workers[19] of 55 per cent in ascitic dogs. Two-thirds of their surviving animals exhibited a marked liver insufficiency which lasted an average of 12 days after which the liver function tests returned to normal. It appears that in most instances deprivation of the main hepatic blood supply—if it does not cause death—does result in parenchymal damage—at least, until such time as enough blood supply becomes available to restore a reasonable level of physiologic function.

At autopsy the liver of these animals was found to be undergoing putrefactive changes. Microscopic examination revealed complete parenchymal destruction, and cultural studies showed uniform findings of anaerobic, spore-bearing bacilli, such as Cl. welchii and B. oedematiens. Desforges[8] came to the conclusion, already advanced by the cultural studies of Romiew and Brunschwiez[28] on liver biopsy specimens taken from patients with and without inflammatory disease of the biliary and gastrointestinal tract, that the normal human liver, in the absence of inflammatory disease, is free of viable bacteria. This is an important concept since it is totally incompatible with the findings noted in experimental animals.

Narath[24] concluded that the hepatic necrosis that followed hepatic artery ligation was due to lack of arterial blood. Following this observation, Markowitz and associates tried to repeat this observation by arterializing the portal blood by various means after effective ligation of the hepatic artery. Their results were conflicting. Assuming that their aseptic facilities were inadequate, they tried to improve the postoperative recovery of their dogs by giving them penicillin. At postmortem examination, much to their chagrin, they found that the anastomatic site was thrombosed, that no arterial blood was entering the portal vein, and that

the liver was normal. They observed that penicillin prevented hepatic necrosis, and concluded that the function of the hepatic artery in the normal dog was to maintain a high oxygen tension to discourage the proliferation of anaerobes, which bring about most of the necrosis. Grant, Fitts, and Ravdin[14] made additional observations using aureomycin with a high proportion of survivals.

Various explanations have been offered to explain why it is not necessary to give antibiotics indefinitely for survival. Eze[11] observed by chance the significant fact that one small dose of penicillin G potassium, which disappears from the plasma in three hours, enables dogs to survive the loss of the hepatic artery. His observations indicate that when the bacterial population of anaerobes is reduced to a sublethal concentration, the defensive forces of the body can resist those that are left. What was puzzling about animals surviving the loss of the hepatic artery was that they continued in good health after the injection of penicillin was stopped. Grindlay and co-workers[15, 16] maintain that this is the result of arterial revascularization during the week of treatment. Since Eze's dogs survived after 1 dose, this explanation does not seem applicable. Although it is the opinion of Rienhoff and Markowitz that antibiotics were of great importance in hepatic artery ligation, Desforges believes that antibiotics are probably of little importance in hepatic ligation in cirrhotic patients. Their chief value appears to be in the prevention of intercurrent infections, such as in the respiratory tract, with their secondary effects on hepatic insufficiency in an already diseased liver.

Intensive antibiotic therapy failed to prevent the progressive hepatic necrosis which followed ligation in case 1 of our series. However, it will be noted that this patient was intensely icteric; had experienced two previous major gastrointestinal hemorrhages; was markedly debilitated by ascites; and exhibited laboratory evidences of hepatic decompensation. Following hepatic and splenic arterial ligation, the initial pressure in the portal vein remained unchanged. This was an ominous finding indicating that the procedure would be without benefit. As anticipated, there was no improvement in the ascites necessitating the insertion of a Patterson button to provide relief from the discomforting abdominal distension. She subsequently developed hepatorenal failure which progressed to the death of the patient four months after ligation.

This case illustrates the dependency upon the collateral circulation to maintain adequate function of the damaged liver cells following the hepatic artery ligation. Survival appears to be directly proportional to the degree of available collateral arterial supply. Michels[22] has shown a remarkable variation in the anatomy of the arterial vasculature in man. In fact, the latter is so extreme that one wonders whether the therapeutic results of a standard ligation operation can ever be predicted. That some kind of compensatory collateral circulation to the liver is established in patients who survive is quite obvious. In a recent publication Michels[23] has shown that there are, at least, 26 possible collateral pathways through which arterial blood may reach the liver. Among these pathways are included collaterals from the right and left gastric, the right and left gastroepiploic, the superior and inferior pancreaticoduodenal, and the superior and inferior phrenic arteries, along with vessels from the intercostals, falciform liga-

CASE I

Mrs. D. K., #877-1 Colorado State Hospital; 43 years, White, Stenographer.
Date of Admission: Aug. 25, 1950

HISTORY: Heavy alcoholism, 10 yrs; 1 pt. wine/day for past year. Jan. 1950: Hemorrhoidectomy; diagnosis of cirrhosis made; medical regimen. Feb. 1950: Ascites; paracentesis, 6000 cc.; hepatosplenomegaly. July 1950: Committed by court order, Denver Gen'l Hosp'l; marked jaundice. Aug. 1950: Adm. Colo. Gen'l Hospital; jaundice, ascites. Apr. 1951: Profuse hemorrhage from dental extraction. June 1951: 1st major hematemesis. Aug. 1951: 2nd massive hematemesis from esophageal varices; 4 days coma due to oversedation; oliguria.

PHYSICAL: Chr. ill; jaundiced. Fluid at both bases. Marked ascites. Spider nevi over chest. Liver 4 cm. below costal margin, hard, nodular. Spleen enlarged.

DIAGNOSIS: Laennec's cirrhosis with esophageal varices and intractible ascites.

OPERATION: Aug. 29, 1951: Ligation of hepatic and splenic arteries. Portal pressure readings:
Preligation: 40 cm. water.
Postligation: 40 cm. water.

RESULT: Ascites recurred. Jaundice increased; urinary output diminished. On the 14th PO day: Fever; thoracentesis, 1300 cc., clear fluid. Oct. 1951: Paracentesis, 8000 cc. Dec. 1951: Paracentesis, 6000 cc., grossly bloody fluid. Dec. 29, 1951: A Patterson button inserted for ascites. Progressive hepatorenal failure. Jan. 1, 1952: Died.

Laboratory Data

| | Preop. | Postop. |
|---|---|---|
| Hemoglobin | 13 | 14 |
| RBC | 3.8 | 4.5 |
| WBC | 10.0 | 12.2 |
| Hematocrit | 50 | 44 |
| Sed. Rate | 19 | 36 |
| Ict. Index | 25 | 21 |
| Dr. Bilirubin | 1.6 | |
| To. Bilirubin | 4.2 | |
| Prothrombin | 36% | 58% |
| Protein | 5.8 | 6.3 |
| Albumin | 2.1 | 1.5 |
| Globulin | 3.7 | 4.8 |
| Cholesterol | 227 | |
| Esters | 92 | |
| Ceph. floc. | 3 | |
| Thymol turb. | 15 | 18.5 |
| BSP (1 hr) | 100% | 66% |

ment, and ligamentum teres. Michels estimated that the incidence of aberrant hepatic arteries was approximately 41.5 per bent. Aberrant right hepatic vessels predominantly arise from the superior mesenteric, less often from the aorta, gastroduodenal, retroduodenal, superficial cystic, or dorsal pancreatic. Aberrant left hepatic arteries arise almost exclusively from the left gastric, or from the superior mesenteric.

It should be emphasized, however, that the blood supply of the liver is always unpredictable and that, because of existent anatomic variation, relatively few of the collateral channels can definitely be relied upon to establish adequate compensatory circulation in the liver when the main hepatic vessel has been ligated. The fact that some patients have survived therapeutic ligation of the common hepatic is counterbalanced by patients in whom the result has been fatal.

## ESOPHAGEAL VARICES

The portal vein, in the opinion of Whipple,[30] carries about 75 per cent of the blood emptying into the liver. This vein carries nutrient material but very little oxygen. For this latter, the liver depends upon the hepatic artery conveying the other 25 per cent of the blood entering the liver. In cirrhosis, the hepatic artery assumes a larger role carrying approximately twice the quantity of blood to the

liver than it does normally. As the portal vein enters the liver, it is subdivided by cords of hepatic cells into sinusoids. These reunite to empty into the hepatic veins and then into the vena cava. This arrangement of veins constitutes the hepatic portal circulation. The relationship between the hepatic artery and the portal vein consists of delicate variations of pressure in an elastic reservoir. The venous blood is supplied at a low pressure (6 to 8 mm. Hg) by way of the portal vein and the arterial blood by high pressure (120 mm. Hg) by way of the hepatic artery. These two systems unite in the sinusoids, and at this point their pressures become equal. The hydrostatic pressure in the normal mesenteric, portal, sinusoidal, and hepatic venous streams progressively decreases from about 26 mm. to 1 mm. Hg. In early portal cirrhosis there is an abrupt fall in the pressure in the sinusoids and the hepatic veins despite the great increase in mesenteric and portal venous pressure. However, in late atrophic cirrhosis, hepatic venous pressure is greatly augmented and is never below the highest normal portal pressure. This, Berman believes, to be due to the many collaterals which pour their contents into the hepatic veins.

The lower end of the esophagus is surrounded by the azygos and hemi-azygos system of veins. Its submucosa is supplied with veins which are poorly supported by surrounding loose connective tissue. These submucosal veins communicate with periesophageal vessels which contribute to the azygos system. Communications between the portal and caval systems occur at this level through anastomosis of the esophageal veins with branches of both the coronary vein and the splenic vein. Any block in the portal system, regardless of its cause, will increase the venous pressure distally. Inability of the muscular and elastic fibers in the walls of the esophageal veins to withstand this pressure results in varices. In cirrhosis this block is intrahepatic and due to the diffuse fibrosis so characteristic of the disease. The intrahepatic portal veins are narrowed and compressed; hence, portal blood reaching the right heart seeks a route that bypasses the liver. One of these routes is through the coronary vein of the stomach to the veins of the esophagus and then through the azygos system to the right side of the heart.

That esophageal varices, the result of collateral blood flow via the coronary-esophageal vein circuit, constitute a potential danger to the patient is common knowledge. The incidence of hematemesis in portal hypertension is 34 per cent; and it has been observed that a patient who had experienced one attack of hematemesis had only a 50 per cent chance of being alive one year later.[6] Prompt transfusion and esophageal tamponage are life-saving measures in the emergency handling of bleeding varices, but the threat of death from a subsequent exsanguinating hemorrhage is still present as long as the portal hypertension remains unchanged. It is, therefore, not only important to control the initial hemorrhage, but also to prevent a fatal recurrence.

Rienhoff[26] believes that portal hypertension is probably significantly reduced in some of the patients following ligation of the hepatic and splenic vessels along with the left gastric artery. In his series of 23 patients, 10 were operated upon primarily for hemorrhage with a mortality rate of 50 per cent in this group. Of the five patients who died, only 2 died of continued bleeding. Two of those who

CASE II

Mr. L. G., #280403 Denver General Hospital; 57 years, Greek, Chef.
Date of Admission: Dec. 14, 1951

HISTORY: Denied alcoholism except for occ. beer; RUQ pain; ascites, 2 mons. pta. Nov. 1950: Bleeding hemorrhoids; constipation; no jaundice. Dec. 1951: Paracentesis, 2000 cc.; Feb. 5, 1952: Paracentesis, 6000 cc.; Feb. 23, 1952: Paracentesis, 5000 cc.

PHYSICAL: Sl. debilitation; no icterus or petechiae; chest clear; marked ascites; liver and spleen not palpable; external hemorrhoids.

X-RAY: Nonfunctioning gallbladder; horse-shoe kidney; marked varices, distal third, esophagus.

DIAGNOSIS: Laennec's cirrhosis with esophageal varices and intractible ascites.

OPERATION: Feb. 29, 1952: Ligation of hepatic, splenic, and left gastric arteries; biopsy of liver. Pressure readings from omental vein:

Preligation: 44 cm. water.
Postligation: 27 cm. water.

RESULT: Mar. 1, 1952: Jaundice; increased ascites. Mar. 15: Massive bleeding; shock; hepatorenal failure. Mar. 20, 1952: Died; acute hepatic failure.

Laboratory Studies

| | Preop. | Postop. |
|---|---|---|
| Hemoglobin | 13 | 11.5 |
| RBC | 4.2 | 3.4 |
| WBC | 6.7 | 19.7 |
| Hematocrit | | 41 |
| Sed. Rate | 0 | |
| Dir. Bilirubin | 0 | 3.5 |
| Tot. Bilirubin | 1.0 | 5.2 |
| Prothrombin | 100% | 47% |
| Protein | 6.6 | |
| Albumin | 3.5 | |
| Globulin | 3.0 | |
| NPN | 40 | |
| Cholesterol | 240 | |
| Esters | 106 | |
| Ceph. floc. | 3 | |
| BSP (45 min.) | 40% | |
| Alk. phos. | 17.5 | 15.2 |

survived had small but definite recurrent hemorrhages. In both of these patients, the bleeding postoperatively was occult with marked change in character; whereas prior to the operation, it was massive and exsanguinating. Portal hypertension, in all probability, was not relieved in those patients who bled to death through hematemesis after the operation.

Although occlusion of the hepatic artery will produce a drop in portal pressure, it is impossible to determine whether or not this decrease will be permanent. In 1 of our cases the procedure did not prevent an initial and fatal hemorrhage. The patient in Case 2 gave no previous history of bleeding, but was known to have esophageal varices demonstrable by roentgenogram. An adequate decrease in venous pressure occurred following the triple arterial occlusion as evidenced by manometric measurement in one of the omental veins. However, jaundice developed during the immediate postoperative period, and hepatic failure ensued. Massive gastrointestinal hemorrhage occurred on the fourteenth postoperative day; and, failing to respond to conservative therapy, the patient rapidly succumbed. Postmortem examination revealed prominent varices in the distal third of the esophagus with evidences of rupture. It is assumed that, despite the adequate reduction in portal pressure which occurred immediately following the legation, this was only temporary and was not sufficient to prevent subsequent bleeding. This case also demonstrates the ineffectiveness and independability of the collateral circulation to adequately oxygenate the damaged liver cells following the ligation, since the patient immediately developed evidences of hepatic failure due to the diminished blood supply.

The operation of triple arterial ligation in the patient in case 3 was beneficial not only from the standpoint of his ascites, but also, thus far—and it is too early to draw a definite conclusion—there has been no recurrence of bleeding. As noted from the summary, he had experienced four major hemorrhages—two of which were massive—requiring approximately 18 pints of blood for stabilization. Although the observation was made by one of us (H. S.) that the prognosis was poor due to the presence of hepatic insufficiency and previous hemorrhages, much to our surprise, he was improved in his physical well-being considerably and there has been no further bleeding episodes. This result appears encouraging; however, we are still dubious concerning the ultimate fate of this patient.

The status of arterial ligation in the prevention of fatal hemorrhage from varices is still in question, and the outcome is difficult to foretell. Madden[20] concluded that hepatic artery ligation has proved ineffective; and, with our unfortunate experience in case 2, we have been forced to the same conclusion. Rienhoff states that, when the common hepatic, splenic, and left gastric arteries were ligated to prevent further bleeding, his results were equivocal and not as successful as those with portacaval shunt procedures.

### INTRACTABLE ASCITES

We are aware that ascites, when once formed, is perpetuated by a combination of many factors, including endocrine, renal, cardiodynamic, nutritional, and local vascular. Yet, it has been demonstrated both clinically and experimentally that the cycle of ascites can be broken, within certain limits, by an alteration in only one of the factors—e.g., the local vascular factor. Herrick[18] concluded from his *perfusion* experiments that in the liver of portal cirrhosis there are more communications between the arterial and portal currents than in the normal liver. He believed that the transmission of hepatic artery pressure to the portal veins through dilated capillary anastomoses in the perilobular fibrous tissues was an important factor in the cause of portal hypertension. Winternitz[31] and, later, Cameron and Mayes[7] also believed that presinusoidal anastomoses existed, but they were unable to demonstrate these channels. Clinical information indicating the presence of presinusoidal anastomoses was supplied by Cohn in a personal communication to Dock[9] who described 4 cases of advanced cirrhosis in which at laparotomy brief occlusion of the hepatic artery by digital pressure caused portal vein pressure to drop as much as 7 to 11 cm. of water. According to Berman normal arteriovenous and venovenous shunts seem to be increased and new short circuits develop in cirrhosis.

Herrick has shown that, in a patient with a normal liver, each rise of 40 mm. of water in arterial pressure causes a rise of 1 mm. of water in portal pressure; whereas, in a patient with cirrhotic liver, each rise of 6 mm. of water in arterial pressure causes a rise of 1 mm. of water in portal pressure. In normal livers, also, he found that arterial pressure increases did not affect portal pressure until the former was greater than 100 mm. Hg. In contrast, this effect was manifest in cirrhotic livers at an arterial pressure of 30 mm. Hg. This mutual influence between the portal and arterial pressure within the liver provides an important explanation for the rise of portal pressure in cirrhosis.

Laufman and associates[19] have shown that ascites accumulation cannot be prevented when only the hepatic artery is ligated, but can be prevented in surviving animals when all of the main hepatic arterial supply is severed. Hence, it appears that there is a direct relationship between the formation of ascites on the one hand and the pressure and oxygen saturation of the hepatic vein blood on the other. Evidence suggests that the more extreme the arterial deprivation of the liver, the better the protection against the reformation of ascites. However, the greater the arterial deprivation of the liver, the higher the mortality.

The hepatic and splenic arteries should always be ligated together in instances of portal hypertension.[27] It has been previously stated that the portal vein pressure is definitely lowered when the hepatic artery is ligated. This pressure still can be reduced further by ligation of the splenic artery. Approximately 1500 cc. of blood pass through the liver per minute. Of this 1500 cc. it has been estimated that the portal vein carries about 75 per cent, of which about 30 per cent comes from the spleen. The rationale, therefore, of ligation of the splenic artery is to diminish the venous return from the splenic vein into the portal. The spleen becomes atrophic and reduces portal pressure by the venous channels which are preserved.

In a recent series of 23 patients reported by Rienhoff, 13 were operated upon for intractable ascites. Of this group 11 were reported as improved while 2 died—a mortality rate of 16.3 per cent. The degree of improvement ranged from that in several patients in whom all evidence of ascites was absent to that in a man who required paracenteses at intervals of six weeks to two months in contrast to once

CASE III

Mr. A. W. H., #41135 Colorado General Hospital; 52 years, White, Printer. Date of Admission: Jan. 14, 1952

HISTORY: Alcoholism, 34 years; increased past 10 yrs. May 1950: Jaundice, malaise. Jan. 1951: Major hematemesis, 18 pts blood. Apr. 1951: 2nd episode of bleeding. May 1951: 3rd episode, bleeding, massive. Aug. 1951: 4th hematemesis. Feb. 1951: Marked asctes. Between Feb. 1951 to Jan. 1952: 20 paracentesis, 5–14,000 cc.

PHYSICAL: Malnourished, weight loss; no jaundice or petechiae. Chest clear. Marked ascites. Liver and spleen not palpable. Hemorrhoids.

X-RAY: Pulsion diverticula, proximal third, esophagus; large esophageal varices, distal third.

OPERATION: Jan. 29, 1952: Ligation of hepatic, splenic, and left gastric arteries; biopsy of liver. Venous pressure, omental vein:

Preligation: 27 cm. water.
Postligation: 27 cm. water.

RESULT: Improved. June, 1952: Had been tapped twice with removal of small amount of fluid; increase in appetite, weight, energy; wears belt size 36 (before OR, size 42). Surgeons note: Prognosis poor due to hepatic insufficiency and hemorrhages preoperatively.

Laboratory Studies

| | Preop. | Postop. |
|---|---|---|
| Hemoglobin | 9.0 | 10.2 |
| RBC | 3.6 | 4.1 |
| WBC | 12.8 | 8.9 |
| Dir. Bilirubin | 0.5 | |
| Tot. Bilirubin | 2.0 | |
| Prothrombin | 56% | 32% |
| Protein | 5.6 | |
| Albumin | 2.8 | |
| Globulin | 2.8 | |
| Ceph. floc. | 4 | |
| BUN | 28 | |
| Alk. phos. | 5.2 | |

## CASE IV

Mr. J. B., #282005 Denver General Hospital; 68 years, White, Unemployed.
Date of Admission: March 7, 1951

HISTORY: Excessive alcoholism, 10 to 15 years; 1 pt. whiskey/day. In 1950, pain RUQ, abdominal swelling due to ascites. Wt. loss, 20 lbs. No jaundice or bleeding. 11 paracenteses during past year, 5,000 to 10,000 cc. Mar. 1951: Punch biopsy of liver, Laennec's cirrhosis.

PHYSICAL: Sl. debilitated; chest clear; no petechiae; marked ascites; no jaundice. Liver enlarged 5 cm. below costal margin, firm, nodular; spleen not palpable; external hemorrhoids.

X-RAY: No evidence of esophageal varices; antral gastritis.

DIAGNOSIS: Laennec's cirrhosis with intractable ascites.

OPERATION: Aug. 16, 1951: Ligation of hepatic, splenic, and left gastric arteries; biopsy of liver. Preligation pressure in omental vein, 40 cm. water.

RESULT: Improved. Feb. 25, 1952: No recurrence of ascites; normal liver function studies; liver biopsy, no significant change from previous biopsies (cirrhosis, Laennec's).

Laboratory Studies

| | Preop. | Postop. |
|---|---|---|
| Hemoglobin | 12.0 | 11.0 |
| RBC | 4.8 | 4.2 |
| WBC | 8.4 | 14.8 |
| Hematocrit | 41 | |
| Sed. Rate | 45 | |
| Dir. Bilirubin | 0 | 0 |
| Tot. Bilirubin | 0.1 | 0.1 |
| Prothrombin | 100% | 81% |
| Protein | 7.0 | 6.5 |
| Albumin | 3.1 | 3.0 |
| Globulin | 3.9 | 3.5 |
| Cholesterol | 148 | 280 |
| Esters | 103 | 152 |
| Ceph. floc. | 3 | 3 |
| Thymol turb. | 5.6 | 3.6 |
| BSP (45 mins.) | 7.5% | 10% |
| NPN | 39 | 44 |
| Alk. phos. | 5.4 | 5.2 |

## CASE V

Mr. T. D., D-12907 General Rose Memorial Hospital; 62 years, White, Meat inspector.
Date of Admission: December 23, 1952

HISTORY: Alcoholism, 20 yrs. Mar. 1951: Weakness, vomiting, malaise, anorexia, ascites. No jaundice or hemorrhage. Paracentesis every 3 weeks, 8–14,000 cc. Inability to work, debilitated. Dec. 1953: Inc. umbilical hernia, reduced spontaneously. Wt. loss, 40 lbs.

PHYSICAL: Debilitated, malnourished. No jaundice or petechiae. Chest clear. Marked ascites. Umbilical hernia, reducible; inguinal hernia, left, reducible. Liver enlarged 5 fb. below costal margin; spleen not palpable.

DIAGNOSIS: Laennec's cirrhosis with intractable ascites.

OPERATION: December 31, 1952: Ligation of hepatic and splenic arteries; biopsy of liver. No pressure studies. Umbilical hernioplasty.

RESULT: Improved. Marked improvement in ascites. In 10 months only 2 paracentesis, minimal amount. Adm. hospital July 1952 for secondary anemia due to severe epistaxsis. Liver studies normal. Gain in weight, strength, and nutrition.

Laboratory Studies

| | Preop. | Postop. |
|---|---|---|
| Hemoglobin | 12.3 | 13.0 |
| RBC | 3.9 | 4.6 |
| WBC | 8.6 | 12.2 |
| Sed. Rate | 30 | 32 |
| Ict. Index | 9.6 | |
| Dir. Bilirubin | 0.3 | |
| Tot. Bilirubin | 0.6 | |
| Prothrombin | 68% | 50% |
| Protein | 6.7 | 7.0 |
| Albumin | 3.3 | 3.8 |
| Globulin | 3.4 | 3.2 |
| Ceph. floc. | 0 | 0 |
| Thymol turb. | 2 | 2.4 |
| BSP (45 mins.) | 38.9% | |
| BUN | 36.3 | 23.2 |
| Alk. phos. | 0.34 | 7.25 |

a week before the operation. It should be stressed that the arterial ligation was successful in reducing the apparently intractable ascites in all of the cases.

Similarly, encouraging results have been noted in our series of cases. In the 3 patients who survived the operative procedure there was considerable improvement in their ascitic condition. In 1 patient (case 4) there was no recurrence of the fluid; while in 2 patients (cases 3 and 5) the rate of reformation was markedly decreased. Prior to operation, the patient in case 3 required a paracentesis every three weeks with the removal of 5–14,000 cc. of fluid; however, during a six month postoperative period, he had been tapped only twice with the removal of small quantities of fluid. The patient in case 5 also had frequent pracenteses with removal of large quantities of fluid preoperatively; while, during a 10 month postoperative period, only two tappings were necessary. Although the formation of ascites was not completely obliterated, reformation was markedly diminished by this procedure. More important, however, is the fact that these patients were no longer disabled and were rendered productive both socially and economically. Their gain in weight, strength, appetite, and feeling of well-being has been most gratifying. The fact that these patients had a minimum of hepatic insufficiency preoperatively was a determining coefficient in their favorable result. Our findings show that the most benefit from the arterial ligation procedure will occur in those patients who present only intractable ascites.

The results of arterial ligation in patients with debilitating ascites, but with good hepatic function appears encouraging, and we believe that the procedure should be continued in this select group of cases. Unfortunately, however, the old adage: "Unstable as water, thou shalt not excel" still applies; and the procedure continues to remain within the realm of palliative or salvage surgery.

## CONCLUSIONS

We have had the opportunity to do arterial ligation in five instances of portal hypertension. The procedure appears to be tolerated by the cirrhotic patient with a minimal functional impairment of the liver; but, since survival appears to be directly proportional to a variable collateral circulation, the effect in each patient is unpredictable.

The operation of triple arterial occlusion has been somewhat disappointing in the prevention of recurrent bleeding from esophageal varices, and the results are equivocal. Although the character of the bleeding may be altered, the danger of a fatal recurrent hemorrhage has not be alleviated.

It is in the group of patients with intractable ascites that the outlook has been more encouraging. Reformation of the ascitic fluid has been either abolished or markedly diminished in all of the patients who have survived the procedure. It is in this group of cirrhotic patients that arterial ligation appears justified as a palliative or salvage procedure.

A review of the experimental and clinical literature that has lead to the development of arterial ligation in portal hypertension has been presented.

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# EVALUATION OF TOTAL GASTRECTOMY WITH ILEO-CECAL TRANSPLANTATION

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## INTRODUCTION

Total gastrectomy was considered quite a surgical feat for many years and, until recently, was reserved for those cases in which only the ultimate in radical gastric surgery was contemplated. Today various clinics show a constantly diminishing mortality rate for total gastrectomy and it has even been recommended as the proper procedure in resectable cases of carcinoma of the stomach. Various reports in the surgical literature give essential information on the technical approach, indications, and salvage rate, but few follow-up studies on patients who had had gastrectomies were done until Paulson[15] in 1951, and McGlone[11] in 1953, reported their findings.

It has long been our opinion that individuals having total gastrectomy and esophagojejunostomy, if carefully followed in the postoperative period, would show that the mortality rate is within acceptable limits, and that the salvage rate is improved because of an earlier and more radical surgical approach, but that the patients are, by and large, *gastric cripples*. We have had the opportunity to follow several patients, who, after having radical surgery for gastric carcinoma have succumbed to complications of the very procedure that, theorectically at least, should have made it possible for them to enjoy a long and happy life. It is these cases, together with those reported by others[3, 4, 8, 9, 14], that have led us to give more serious consideration to ileocecal transplant as a valuable technical and physiologic adjunct to the treatment of gastric carcinoma and other perplexing and serious lesions of the stomach.

## CLINICAL MATERIAL

The clinical material presented comprises 16 cases of total gastrectomy with ileocecal transplants (procedure as described by Lee[8]). This group is compared to McGlone's series of 20 cases of total gastrectomy without transplant. Of the 16 cases of ileocecal transplant, there was one immediate postoperative death. Two patients were subjected to this radical procedure for benign gastric lesions; i.e., polyposis of the stomach and recurrent marginal ulcer (figures 1 to 4).

Table I summarizes 16 cases of total gastrectomy with ileocecal transplants, 13 of which were done by us and the remaining 3 by other members of the Staff.*

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* Drs. Kenneth Sawyer, George Wollgast, and Karl Sunderland, to whom we express our sincere thanks and appreciation for the privilege of including their cases in this study.

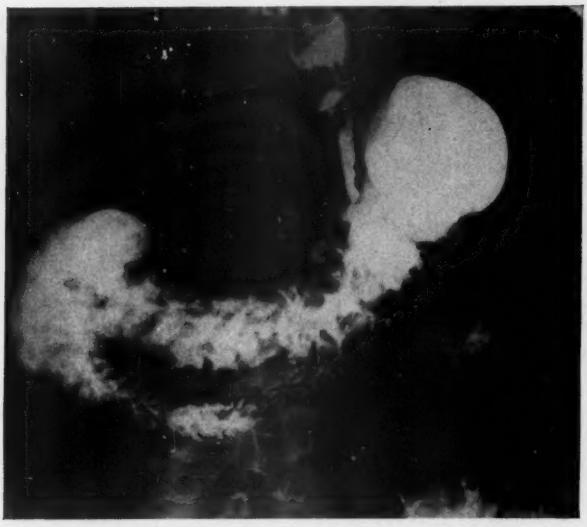


FIG. 1. A 10 day roentgenologic study of a cecal pouch taken 10 ninutes after the ingestion of barium.

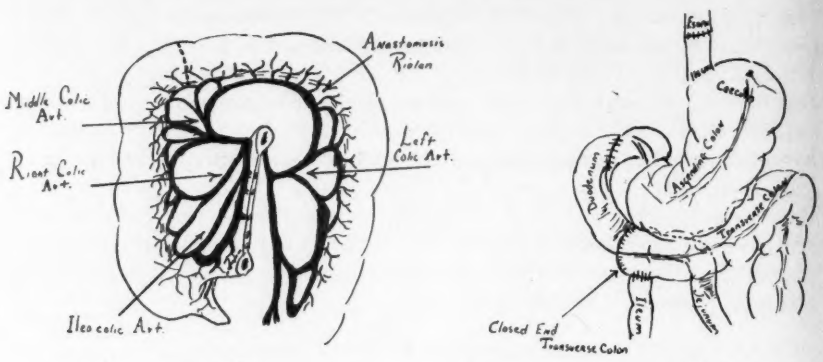
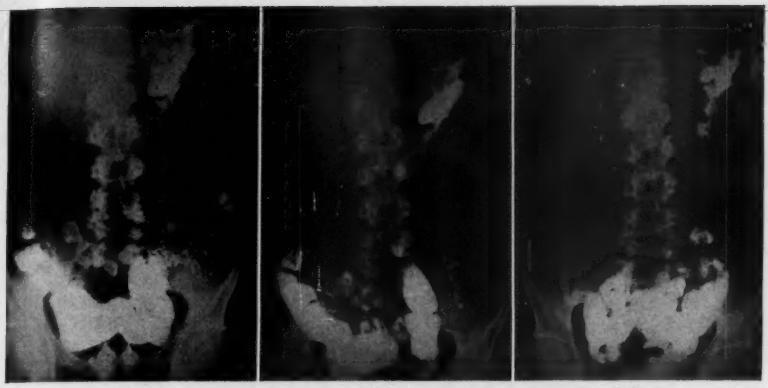



FIG. 2. Outline drawing (after Lee) demonstrating area of resection at ileum and in transverse colon with rotation of the segment to produce esophagoileostomy, duodenocolostomy and re-establishment of large bowel continuity by ileotransverse colostomy.

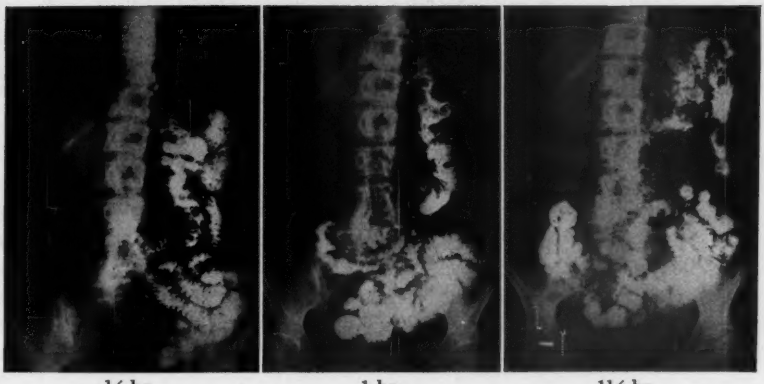
Of the 16 patients, 12 are living, 2 with evidence of distant metastases. The four deaths were caused by (1) acute fulminating pancreatitis in the immediate postoperative period, (2) acute congestive heart failure occurring nine weeks after operation, and (3) and (4) distant metastases.

Table II summarizes for comparison the cases previously presented by McGlone.[11] Of the 20 patients having total gastrectomy, 2 had gastrodudenostomy, and the remaining 18 a gastrojejunostomy as the procedure for re-establishment



1 hr. 1½ hr. 2 hr.

FIG. 3.



½ hr. 1 hr. 1½ hr.

FIG. 4.

FIGS. 3 and 4. Late postoperative roentgenograms (3 to 4 months) demonstrating reservoir action of ileocecal transplant.

TABLE I

*Total gastrectomy with ileocecal transplant*

| Diagnosis | Number | Hospital Deaths | Postoperative Course |
|---|---|---|---|
| Carcinoma | 14 | 0 | Good—13<br>Fair—1<br>Of the 12 surviving patients: Weight gain from 10 to 15 pounds has been noted. All patients have shown good appetites. Two patients dying of metastases had no late or terminal digestive difficulties. |
| Polyposis | 1 | 0 | This patient has gained 45 pounds, has no anemia or gastrointestinal difficulties. |
| Postgastrectomy Cachexia | 1 | 1 | Died 38 hours after operation of acute fulminating pancreatitis. |

TABLE II

*Total gastrectomy without ileocecal transplant*

(Modified from McGlone)

| Diagnosis | Number | Operative Deaths | Postoperative Course |
|---|---|---|---|
| Carcinoma | 12 | 8 | Only 1 surviving patient is without nutritional problems |
| Gastric ulcer | 6 | 2 | 1 death—6 months<br>1 death—18 months } malnutrition |
| Postgastrectomy Problem | 1 | 1 | — |
| Polyposis | 1 | 1 | — |
| Polyadenosis | 1 | 1 | — |

Note high early and late mortality rates of resection for benign lesions in this series.

of gastrointestinal continuity. In this series there were 13 deaths, three of which, on postmortem examination, showed no evidence of neoplasm. Death was attributed to malnutrition.

## DISCUSSION

It is now an accepted fact that the surgical contribution to an improved salvage rate in gastric cancer is due, at least in part, to wide resection of the neoplasm, contiguous tissue and regional lymphatics. The stomach, however, is not an organ that always lends itself to this kind of dissection because of its extensive lymphatic drainage. Reports by Lahey,[5, 6, 7] and others[2, 5, 7, 10, 12] have indicated that the salvage rate is somewhat increased in resectable patients having total gastrectomy.

As previously indicated, not too much attention has been given to the nutritional problems that develop in the patient who had total gastrectomy. Following the reports of Paulson[15] Hunnicutt[4], and Lee[8], working independently, developed a procedure which was designed not only to accomplish wide resection of the tumor and contiguous tissue, but to maintain as nearly as possible the original continuity of the upper gastrointestinal tract. It has been our experience, as well as that of others,[1, 4, 8, 11, 13] that one must consider not only adequate resection of the lesion, but the recovery of the patient to a relatively normal existence. That the individual should suffer esophagitis, *dumping*, or obstruction, or even succumb at a later date to inanition is regrettable and, we believe, avoidable. A variation of the old adage: "The operation was a success but the patient died" may, in the case of esophagojejunostomy, be changed to "The patient recovered but is a gastric cripple". In one of McGlone's patients death occurred after 18 agonizing months of repeated hospitalization for incomplete obstruction, esophagitis, and *dumping*. At autopsy examination no evidence of recurrent carcinoma could be found. The cause of death was given as malnutrition.

In addition to the above distressing and, at times fatal sequelae, a patient

deprived of his gastric reservoir may find it very difficult, if not impossible, to function as a self-supporting social unit when faced with the problem of attempting to maintain an adequate caloric intake on 8 to 10 feedings per day. Some reports on the results of total gastrectomy would indicate that such apparently is not too much of a problem.[5] However, as emphasized in table II, not all such patients fare so well. A sedentary occupation may more naturally lend itself to a regimen of frequent small feedings, but gastric cancer has no particular predilection for the banker, accountant or bookkeeper.

The satisfactory clinical results in our group of patients give further impetus to the conclusion of Lee[8] and McGlone[11] that admixture of the food high in the intestinal tract, temporary interruption of the food bolus prior to its entrance into the small bowel, and the ability of the patient to enjoy his meals are of great importance in successful nutrition to say nothing of the enjoyment of life.

Improvements in technic and adequate preoperative and postoperative care place the procedure of ileocecal transplant from the mortality rate standpoint in a favorable position when compared to other types of reconstruction following major resections of the stomach.

While the series presented is obviously small, the mortality rate and morbidity are acceptable and should give considerable support to more frequent consideration of total gastrectomy with ileocecal transplant in all cases of resectable gastric carcinoma and radical surgery for benign lesions where only a small cuff of proximal stomach could be retained for anastomosis.

Because of discouragement, both with the distressing after effects and the still relatively low salvage rate of classical types of total gastrectomy, many surgeons have elected to do partial gastrectomy.

We are well aware that it is impossible in most instances for the surgeon completely to eradicate a gastric cancer in spite of (as is our policy) total gastric resection with a few inches of the esophagus, several centimeters of the duodenum, the greater omentum, spleen, excision of the gastrohepatic ligament as close to the liver as possible, the tail of the pancreas, and ligation and excision of the splenic vessels and the left gastric artery at the celiac axis. An inadequate surgical procedure is not only a compromise but will contribute nothing toward the solution of gastric cancer. Reconstruction with ileocecal transplant appears adequately to solve the *gastric cripple* aspect of total gastrectomy, and should allow further exploration of the value of radical gastric resection in the treatment of malignant and extensive benign lesions of the stomach.

## SUMMARY AND CONCLUSIONS

Sixteen cases of ileocecal transplantation are presented. The results are compared with a previous series of 20 cases of total gastrectomy compiled by McGlone.

The problems attendant on total gastrectomy with esophagojejunostomy or esophagodudenostomy are many and serious, often resulting in a *gastric cripple.*

The advantages of adding ileocecal transplantation to total gastrectomy are presented.

A more critical long term follow-up of patients receiving total gastrectomy with so-called conventional anastomoses is suggested.

Further study of the use of the ileocecal transplant in the treatment of gastric carcinoma and extensive benign lesions of the stomach is recommended.

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# CONGENITAL BOWING OF THE TIBIA ASSOCIATED WITH NON-OSTEOGENIC FIBROMA

## REPORT OF A CASE

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The problems of congenital bowing of the tibia have been presented in several recent articles.[1, 4, 6, 8, 10, 11] Most authors consider this deformity to be a transient one leading to pseudarthrosis of the tibia following pathologic fracture or injudicious osteotomy. Indeed, Moore[11] has classified congenital bowing as prepseudarthrosis of the tibia. The work of Duraiswami[3] has aroused renewed interest in the etiology of this anomaly and other congenital skeletal defects. Some authors[2, 5] have considered congenital bowing of the tibia to be a manifestation of neurofibromatosis. Another case report would be valueless were it not for the interesting coincidence of features in the patient. No information about the etiology of congenital bowing is apparent in this case, but the transition of the deformity toward pseudarthrosis is well demonstrated.

### CASE REPORT

Baby boy, S. G., was born in the Colorado General Hospital on June 27, 1948, without difficulty or trauma at the time of delivery. The birth weight was 3827 Gm. During pregnancy the child's mother had been well and had had no injuries. Her diet apparently was adequate. The mother had had one previous pregnancy, and the child of her first pregnancy was entirely normal. The parents were Negro, and there was no consanguinity. Serological examinations of both parents and the patient were normal.

Notes in the chart of S. G. at the time of admission to the newborn nursery, and again at the time of his discharge from the hospital, state that the physical examination was normal. He was seen in the well baby clinic on four different occasions by four different physicians, and the notations were made that the examinations showed no abnormalities. The first notation of abnormality was made when the child was 5 months old. At that time the physician stated that the "left leg shows angulation near the ankle joint resembling a healed fracture." The mother stated that this angulation had been apparent to herself and other observers for at least two months. Shortly after the birth of the patient, the mother had the impression that the legs were bowed. However, she believed that the curvature was bilateral. Not until the patient was 3 months old were the parents certain of deformity of the left tibia. All concerned with the care of the patient denied any trauma.

At this time (November 1948) a thorough physical examination was made.

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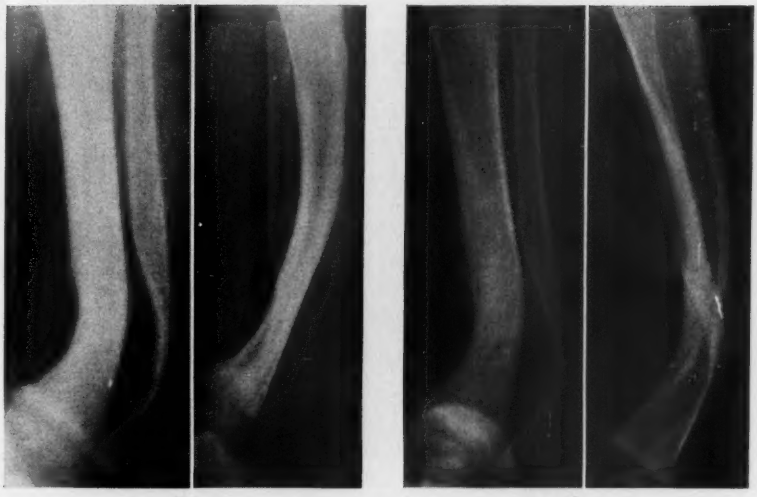
Numerous small punctate and geographic areas of hyperpigmentation were found over the entire body which, in retrospect, were thought to be *cafe au lait* markings. No neurofibromata were found. The remainder of the examination, with the exception of the left leg, was normal. Compound bowing of the left tibia and fibula in the distal portion of the middle third was evident with the convexity anteriorly and laterally. There was no tenderness, swelling or discoloration. The Achilles tendon was not shortened. The skin over the deformed tibia was normal. Roentgenograms were made (fig. 1-a) and interpreted as showing localized osteogenesis imperfecta. Roentgenograms of the remainder of the skeleton were normal. Serum calcium, phosphorus and alkaline phosphatase determinations were normal. The acid phosphatase was elevated (9.3 King-Armstrong units). The final diagnostic impression was that the deformity represented an isolated congenital anomaly rather than osteogenesis imperfecta or neurofibromatosis. No therapy was recommended.

Serial roentgenograms demonstrated slight progression in the curvatures of the left tibia and fibula (fig. 1). When the child began to stand, a long leg brace with a leather cuff over the apex of the curvature was prescribed. He was able to walk and play at the age of 13 months.

In January 1950, when the child was approximately 1½ years old, he was hospitalized at the Denver General Hospital because of pain in the left leg following trauma. Roentgenograms did not demonstrate a fracture. Serum calcium and phosphorus determinations were again normal. The alkaline phosphatase was 9.1 Bodansky units; the acid phosphatase 0.6 Bodansky units. No therapy was provided since the pain quickly subsided with bed rest. The patient was discharged from the hospital wearing the long leg brace.

On April 6, 1952, when the child was 3 years and 10 months old, he fell down a flight of stairs while on the way to bed and not wearing his brace. At this time roentgenograms revealed a fracture of the tibia through an area of diminished density in the distal portion of the curvature (fig. 2). This area of diminished density had first been noted in the distal tibial epiphysis in November 1950 (fig. 1-c). Then the area was considerably distal to the endosteal sclerosis of the cortex of the concave aspect of the deformity. In subsequent roentgenograms, this area of radiolucency had approached the area of osteosclerosis. At the time of the pathologic fracture the serum calcium, phosphorus and alkaline phosphatase determinations were normal. On April 19, 1952, an autogenous fresh graft was removed from the mid portion of the right tibia and transplanted to the concave aspect of the deformed left tibia. In an irregular saucer-like depression in the posterior and medial aspect of the left tibia distal of the apex of the curvature was found a mass of friable greyish-yellow tissue. It was covered only by periosteum, and was removed with a curet. The grafts were not placed as far distally as was desired because placing the grafts distally beyond the saucer-like depression would not permit their contact with the host tibia at the apex of the curvature. The periosteum could not be closed over the grafts. Following the operation, recovery was without complication, and the patient was discharged from the hospital wearing bilateral long leg plaster dressings (fig. 3-a).



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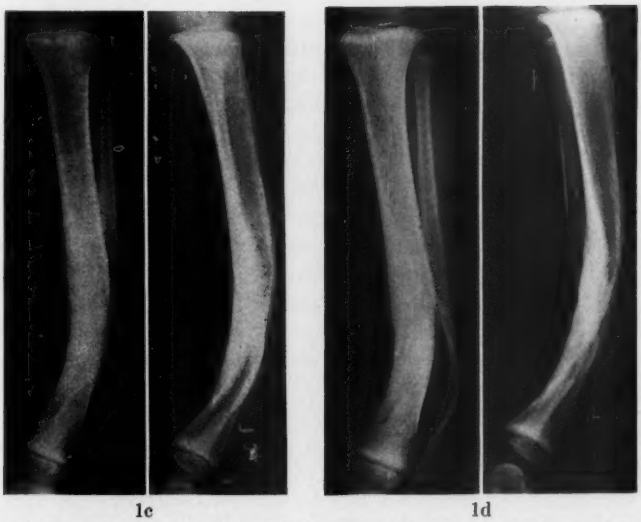

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FIG. 1a. Roentgenograms Nov. 24, 1948. Compound bowing of the tibia and fibula at the junction of the middle and distal thirds. Note the constriction at the site of bowing and the absence of sclerosis at the site of bowing.

FIG. 1b. Roentgenograms May 26, 1949. Patient at this time standing and walking. Note the marked endosteal bone proliferation on the concave cortex at the apex of the curvature.

FIG. 1c. Roentgenograms Nov. 7, 1950. Note the two areas of radiolucency in the fibula and the one in the distal tibial metaphysis.

FIG. 1d. Roentgenograms April 10, 1951. The distal tibial and fibular epiphyses have grown away from the previously noted areas of radiolucency. In the lateral view, the lesion lies in the posterior cortex.

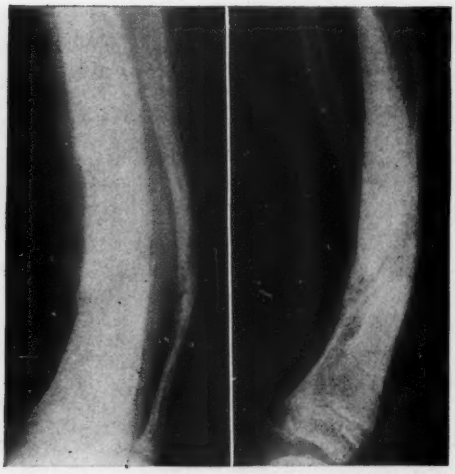


FIG. 2. Enlarged roentgenogram April 17, 1952, showing the apex of the curvature. Area of diminished density now at the lower border of the endosteal sclerosis. Pathologic fracture is through this area.

Microscopic sections of the friable tissue removed from the depression in the posterior cortex of the left tibia are shown in figure 4. These show mature fibroblasts with little collagen formation, disseminated multinucleated cells and phagocytic cells with pigment deposits. No osseous metaplasia was present in the lesion itself. However, other sections showing the junction of the lesion with periosteum show reactive bone formation in the latter. Macrophages are not the prominent cell type in the tissue. No lipoid filled marcrophages were seen. This lesion was called a nonosteogenic fibroma by Jaffe and Lichtenstein.[9]

In August 1952, the plaster dressings were removed. The donor tibia demonstrated excellent repair and immobilization was discontinued (fig. 5-c). Subsequently, the patient was permitted to bear full weight on this tibia. No motion was apparent in the left tibia (fig. 3-b), and a new long leg brace was prescribed for this extremity. However, following minor trauma while wearing the brace, the left tibia soon refractured and became displaced. Closed manipulation of the fracture was unsuccessful. On Oct. 22, 1952, a sliding graft was removed from the anterolateral aspect of the left tibia and placed across the fracture site. Other bone removed from the convex portion of the curvature was packed about the fracture site. The fracture was stabilized with a single screw. Tissue for a biopsy taken from the original graft showed excellent creeping substitution and osteogenesis. Again the convalescence was without complication, and the patient was discharged from the hospital wearing a long leg plaster dressing on the left (fig. 3-c).

In January 1953, the screw was removed. The plaster dressing was continued until August 1953, at which time roentgenograms demonstrated solid union of the fracture (fig. 3-d). There was 1 centimeter of shortening of the left lower

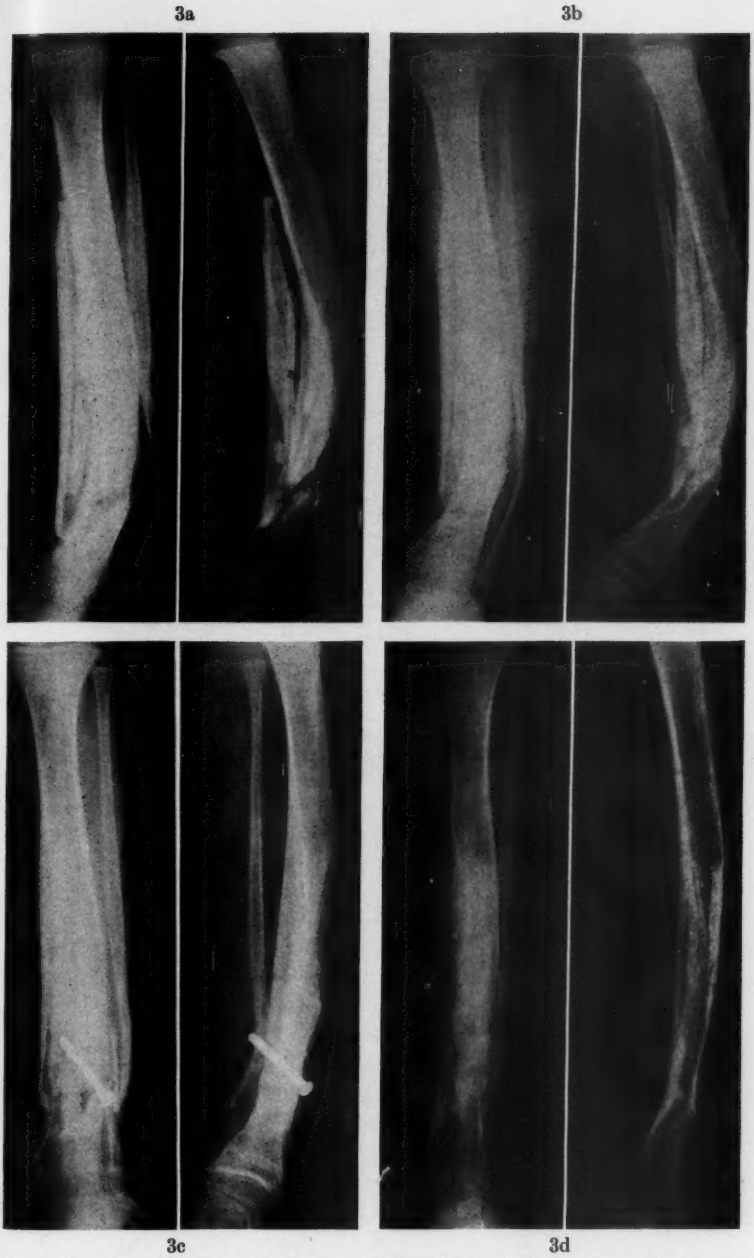



FIG. 3a. Roentgenograms May 10, 1952. Made three weeks following the original operation showing position of the grafts, and early union of the grafts to the host tibia.

FIG. 3b. Roentgenograms Aug. 8, 1952 showing excellent incorporation of the grafts and probable union of the fracture. Note the atrophy of the endosteal sclerotic mass.

FIG. 3c. Roentgenograms Dec. 2, 1952, following the second operation and demonstrating the sliding intramedullary graft, onlay grafts and the screw fixation. Note the displacement of the fracture of the fibula and the loss of the endosteal sclerotic mass in the tibia.

FIG. 3d. Roentgenograms Aug. 18, 1953 which show union of the fracture and incorporation of the grafts with the formation of a new medullary canal. Note the nonunion of the fibula.

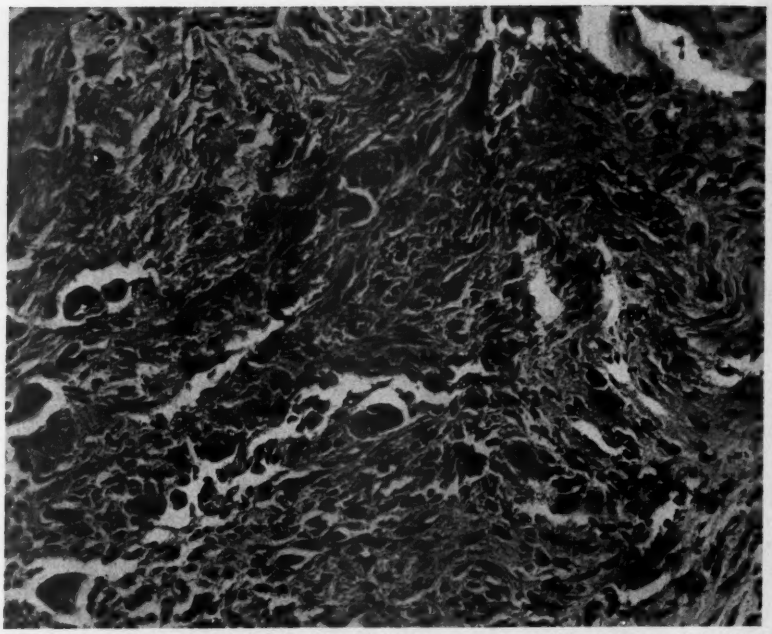
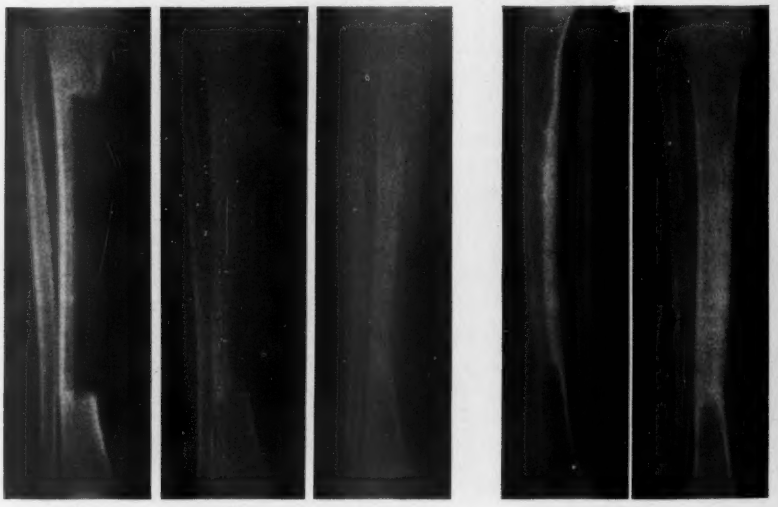


FIG. 4. Photomicrograph (250 ×) of the friable tissue removed from the area of diminished density showing mature fibroblasts, scattered multinucleated cells and a few macrophages.



5a 5b 5c 5d

FIG. 5a. Roentgenogram of the donor tibia May 10, 1952, three weeks after removal of the graft.

FIG. 5b. Roentgenogram (donor tibia) June 27, 1952, nine weeks after removal of the graft.

FIG. 5c. Roentgenogram (donor tibia) Aug. 8, 1952, at which time the plaster dressing and immobilization were discontinued.

FIG. 5d. Roentgenograms (donor tibia) Aug. 18, 1953, 16 months after removal of the graft.

extremity. Slight anterior bowing of the tibia was still evident. The patient was placed in a long leg brace with a short leg leather cuff. The child appeared normal and enjoyed normal activity.

## DISCUSSION

This patient presents all of the well known diagnostic features of this deformity as noted by previous authors.

Although the deformity probably was present at birth, it apparently was so mild that it escaped detection by examining physicians. The mother's original impression was that both legs showed bowing again indicating the mildness of the curvature. When the first roentgenograms were made at the age of 5 months, the deformity already was well established. There was little increase in the curvature until pathologic fracture occurred.

Badgley[1] has emphasized the appearance of the constriction at the site of the curvature and the endosteal sclerosis of the cortex of the concave aspect of the tibia. Often this sclerosis is sufficient to obliterate the medullary cavity at the apex of the curvature. In this patient, the constriction at the site of bowing was present in the original roentgenograms, but the endosteal sclerosis did not appear until the child began to bear weight on the extremity. This sclerotic bone became atrophic with disuse and disappeared as the posterior graft united with the host tibia and assumed functional weight bearing. The most recent films in August 1953 (fig. 3-d), show re-establishment of the medullary canal of the left tibia with the bone graft as the posterior boundary and the original posterior cortex as the anterior boundary of the canal. There now is minimal endosteal sclerosis upon the bone graft which is the concave aspect of the residual curvature. This may represent the beginning of another cycle of this endosteal mass.

Frequently mentioned by the radiologists in their reports on this deformity have been *cystic* areas. These do not represent true bone cysts, but are merely radiolucent tissue. In this patient a nonosteogenic fibroma produced the area of diminished density. This lesion is not a benign neoplasm as the name would indicate, but probably the result of some insult to the zone of enchondral ossification on the metaphyseal side of the cartilaginous epiphysis. The evolution of this lesion and its ultimate fate have been well presented by Hatcher[7] and Ponsetti.[12] The concept is that this lesion remains stationary while the epiphyseal cartilage grows away from it. As the metaphysis is remodelled into diaphysis, the lesion becomes superficial and may eventually disappear. This has been termed the *healing out* stage of the lesion. In this patient it is very interesting that the nonosteogenic fibroma and the apex of the curvature approached each other, indicating that the curvature progressively involved more of the tibia or that it migrated distally with patient growth.

The tendency for pathologic fracture and the potential danger of nonunion in patients with this type of curvature is demonstrated by this patient. Pseudarthrosis of the fibula is apparent at the present time. On the other hand, the rather prompt union of the tibia on two occasions would indicate that local bone formation is adequate and surgical procedures are not doomed to failure. That this

patient cannot be considered cured is evident in a study of the most recent roentgenograms. These films show excellent position and union in the anteroposterior view, but the lateral view demonstrates new minimal endosteal sclerosis upon the cortex of the concave side of the residual curvature. Curiously, this concave cortex represents the original bone graft. In addition, the angulation of the distal tibial epiphysis in the lateral views has increased when compared with prior films. These features well may represent recurrence of the deformity.

Of surgical interest is the rapid and complete repair of the donor tibia indicating that there is no generalized defect in bone formation. Roentgenograms of the donor tibia are shown in figure 5. After removal of the graft, the tibial crest and lateral cortex alone remained. Within four months new bone formation had almost filled the defect. Sixteen months after removal of the graft, a medullary canal had formed in the donor tibia, and its strength appeared to be as great as normal.

## CONCLUSIONS

One case of congenital bowing of the tibia (kyphoscoliosis) is presented showing the progression of the deformity.

Pathologic fracture occurred, but union of the fracture followed the use of autogenous fresh bone grafts.

Fracture occurred through a nonosteogenic fibroma which had approached the apex of the curvature through differential growth.

*Cystic* areas mentioned by previous authors represent merely radiolucent tissue, which may be a nonosteogenic fibroma.

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# EMULSIFIED FAT IN NUTRITIONAL MANAGEMENT FOLLOWING MASSIVE RESECTION OF SMALL BOWEL

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The literature continues to show scattered case reports of massive intestinal resection since Haymond's collective review in 1932.[8] Mersheimer and associates[9] in a recent review of the literature state there are about 212 cases of successful resections recorded. Recently more attention has been directed to metabolic studies[1, 2, 4, 11, 12] and the problem of maintaining these patients with a diet that is adequate for nitrogen equilibrium and yet is still palatable. Reported here is another case of massive small bowel resection with a discussion of the dietary problem involved in the postoperative management.

## CASE REPORT

This 60 year old Spanish-American man entered the hospital on Dec. 12, 1952 complaining of lower abdominal pain. Five hours prior to admission, the patient's lower abdomen became tender and rigid. This was associated with severe sharp constant abdominal pain with an urge to defecate. He had a normal bowel movement at that time and the pain subsided. He vomited one time prior to admission. The past history revealed that approximately 10 years prior to admission, the patient had consulted his doctor because of shortness of breath and ankle edema. He was given some *pills* which he continued to take for a short period of time. Thereafter, he did not seek further medical aid until two years ago, at which time again he was placed on medication for the same trouble. He worked in spite of moderately severe dyspnea until one year ago when dyspnea and orthopnea increased in severity.

*Physical Examination:* Patient was a well developed, well nourished man in no acute distress with a blood pressure of 150/100 and an irregular pulse (auricular fibrillation was confirmed by EKG). The abdomen was slightly distended with minimal generalized tenderness. Bowel sounds were present. A roentgenogram of the abdomen was negative at that time.

Within the next 24 hours, the patient passed several grossly bloody stools. The abdomen became distended and tender throughout. Roentgenograms of the abdomen now showed dilated loops of small bowel which were interpreted as indicating small bowel obstruction.

Laboratory studies at this time revealed a hemoglobin of 13.5 Gm per cent, white blood cell count of 17,400 cells per cm. with 78 per cent polymorphonuclear

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TABLE I

| Post-operative Day | Date | Diet | Serum Chemistries | | | | | Intake (24 hrs.) | | | | Tolerance of Diet | | Body Weight (in Pounds) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $Cl^-$ | $CO_2$ | $Na+$ | $K+$ | Protein | Cal. | Carbo-hydrates | Fats | Pro-teins | | | |
| 7 | 12-15-52 (Surgery) | $H_2O$ and Salts | 101 | 43% | 137 | 6.7 | | 1200 | 300 | | 150 | Diarrhea | Vomiting | 180 |
| | 12-22-52 | | 96 | 32% | 133 | 4.7 | | 800 | 150 | | 50 | | | 165 |
| 8 | 12-23-53 | Surg. Liq. and Skim Milk | 113 | 35% | 134 | 5.6 | 6.9% | 1500 | | | | 4+ | 1+ | 157 |
| 12 | 12-26-52 | | 107 | 19% | 134 | 5.2 | 6.2% | 1000 | | | | (10-15/d) | | |
| 13 | 12-26-52 | Full Liquid | 108 | 38% | | | | 2225 | 230 | 75 | 115 | 4+ | 2+ | 155 |
| | 12-27-52 | | | | | | | | | | | (10-15/d) | | |
| 14 | 12-28-52 | Full Liquid and Formula I | 104 | 25% | | | | 4725 | 413 | 240 | 186 | 4+ | 0 | 155 |
| | | | | | | | | | | | | (10-15/d) | | |
| 15 | 12-29-52 | Formula II | 117 | 33% | | | 5.9% | 1537 | 168 | 96 | 35 | 2+ | 0 | 152 |
| 17 | 12-31-52 | | | | | | | | | | | (3-6/d) | | |
| 18 | 1-1-53 | Soft Diet and Formula II | | | | | | 3522 | 403 | 181 | 105 | 2+ | 1+ | 150 |
| 22 | 1-5-53 | | | | | | | | | | | (4-5/d) | | |
| 23 | 1-6-53 | Soft Diet, Formula III & Amino Acids | | | | | | 3682 | 403 | 181 | 145 | 3+ | 1+ | 151½ |
| | | | | | | | | | | | | (5-10/d) | | |
| 24 | 1-6-53 | Same | 107 | 38% | 130 | 5.6 | 6.2 | | Same | | | 2+ | 2+ | 150 |
| 30 | 1-13-53 | | | | | | | | | | | (4-5/d) | | 156 |
| 31 | 1-14-53 | Pureed Food, Formula III | | | | | 6.31 | | Same | | | 0 | 0 | 155 |
| 37 | 1-20-53 | & Amino Acids | | | | | | | | | | (0-2/d) | | |
| | 1-20-53 to 9-2-53 | Regular Diet and Formula III | | | | | | | Same | | | 0 (3-4/d formed) | 0 | 159 |

Intravenous fluids consisted of 5 per cent dextrose in water, 5 per cent dextrose in 0.9 per cent sodium chloride; added to these were various amounts of Vitamin B, Vitamin C, and potassium chloride.

Formula number I: Lipomul (Upjohn) 250 cc., milk 1,000 cc., eggs 6, corn syrup 150 cc., 100 mg. of Vitamin C, B Complex 4 cc., NaHCO 5 Gm., NaCl 2 Gm., Oleumpercomorphym (Mead-Johnson) 0.6 cc. Furnishes six feedings of 200 cc. each. Total amount of calories: 2500.

Formula number II: Lipomul (Upjohn) 250 cc., Somagen (Upjohn) 50 Gm., corn syrup 180 cc., water 1,000 cc. Furnishes six feedings of 225 cc. each. Total calories: 1500.

Formula number III: Lipomul (Upjohn) 250 cc., chocolate proteinum (Mead-Johnson) 50 Gm., corn syrup 180 cc., vanilla flavoring 4 cc., 2 tablespoonsful of Stuart's Amino Acids (The Stuart Company, Pasadena, California) (may be given separately with fruit juices), water 1,000 cc. Furnishes three feedings daily. Total calories: 1500.

leukocytes. Urinalysis showed 2 plus albumin, and an occasional white blood cell per high power field. Blood non-protein nitrogen was 43 mg. per cent; serum chloride, 101 mEq/L; serum amylase, 259 per cent of normal. The impression at this time was that he had a mesenteric thrombosis, and accordingly operation was done.

*Operation:* Under general anesthesia a right rectus muscle-splitting incision was made. A moderate quantity of seropurulent exudate was noted on entering the peritoneal cavity. The small bowel was gangrenous throughout most of its extent. An extensive resection of the small bowel was done leaving approximately 5 inches of jejunum and 10 inches of terminal ileum. The abdomen was drained with two Penrose drains and the incision was closed with through and through sutures of no. 28 stainless steel wire.

*Pathologic report:* "Specimen consists of a 300 cm. segment of small intestine with attached mesentery. The mesenteric artery is occluded with dark red adherent clot and the small intestine gives the appearance of a recent infarction throughout."

*Postoperative course:* The patient was given only parenteral fluids the first seven days after operation. Nasal suction was discontinued at that time. The patient was given dicumarol on the first postoperative day, and has continued on a maintenance dose to the present. A diet consisting of fluids was started on the eighth postoperative day (table I) and was advanced slowly until the eighteenth postoperative day at which time he was given a soft diet plus a supplementary formula. As can be noted in the table, varied types of formulas in conjunction with the diet were used until one was found that the patient could tolerate best with the least diarrhea and gastrointestinal upset.

On the thirteenth postoperative day the patient's serum calcium and phosphorous were within normal limits. At no time was there any clinical evidence of hypocalcemia. He began to gain weight on the twenty-fourth postoperative day and has maintained his weight to the present.

He has been observed in the out-patient department at weekly intervals and is now on a selective regular diet supplemented with formula no. 3 (table I). At present, Oct. 28, 1953, he has three to four formed stools a day which are not frothy or excessively large. Since the patient still has auricular fibrillation he continues to take a maintenance dose of dicumarol.

## DISCUSSION

Bryant[3] states that the length of the small bowel varies from 10 feet (264 cm.) to 28 feet, 4 inches (863 cm.). According to Cogswell[5] and Sawyer,[10] massive resection means that 200 cm. or more of small bowel has been removed. However, we believe that one should be more concerned with the length of small bowel that remains after resection, since the normal length as already stated varies so much. We therefore should like to propose the following definition: Massive resection is the removal of all of the small intestine except the proximal portion down to 50 cm. or less below the ligament of Treitz. Flint[6] in a study on dogs, found that the absorbing surface of the remaining intestine increased approximately

400 per cent after massive resection of the bowel. In attempting to carry on its functions, the remaining small bowel after resection in man also probably hypertrophies.

After massive resection, carbohydrates are absorbed most efficiently, and fats the least. It is thought that fats are hydrolyzed adequately but are not absorbed. Althausen[1] found that 100 per cent of carbohydrates, 62 per cent of proteins and 23 per cent of fats were absorbed. After placing a patient with massive resection on both natural and synthetic diets, he concluded that the clinical advantage of predigested or synthetic food stuffs was of limited scope. Berman[2] confirmed Althausen's data on the absorption of carbohydrates, proteins and fats.

One of the most difficult problems in the postoperative management of patients with massive resection of their small bowel is to attain positive nitrogen balance. This depends to a large extent on an adequate caloric intake. This in turn depends upon adequate absorption and utilization of fat and, at the same time, the avoidance of gastrointestinal upset.

Frazer[7] stated that there were two mechanisms present in the absorption of fat: (1) The classical lipolytic theory of fat absorption and (2) fat as neutral fat in finely emulsified form, with particles of 0.5 to 1.0 micron in diameter, which passes directly through the intestinal mucosa into the lacteals, thence via the lymphatic channels and the thoracic duct to the bloodstream.

Whole milk is almost nutritionally complete with a high caloric value, and is relatively economical. It contains 4 per cent fat. Case[4] found that fat particles in whole milk varied from 1.0 to 18.0 microns in size with an average of 4 microns while in homogenized milk they varied from 0.5 to 2.0 microns with an average of 0.75 microns. Case then used *spans*, which are emulsifying and wetting agents, to increase the per cent of fat in milk to 6, 8, and 12 per cent. He found that this increased percentage of fat content increased intestinal motility and, resulted in failure to utilize the added calories. Maximum benefit from administered fat is obtained, however, if an emulsifying and wetting agent is used. In regard to the addition of extra protein to a feeding, Case noted that when the basic minimum of calories is provided (as in homogenized milk) the higher the added protein intake, the greater will be the positive nitrogen response, without regard to caloric intake.

With these findings in mind, we elected to incorporate emulsified fat into the formulas which we gave our patient. Formulas I, II and III all utilized Lipomul* for this purpose. The feedings should be small and frequent so that the remaining intestine is being constantly utilized. The formula is taken three times a day between the regular meals. Supplementary feedings of synthetic foodstuffs must be palatable and not cause anorexia. Otherwise, the advantages to be gained by such a feeding are offset by the diminished intake of the patient's regular meals. The use of one formula for supplementary feedings in all patients is not possible and, as in this case, frequent alteration of the formula may be necessary until

* Upjohn Co., Kalamazoo, Mich. Lipomul: 40 per cent peanut oil, 10 per cent sucrose, 2.2 per cent emulsifier, 7.3 mEq. of sodium per liter, 8.0 mEq. of potassium per liter. Stable for months at room temperature. Contains 4 calories per cc. Particle size of oil dispersion .5 to 1 micron.

one is found that does not cause anorexia. In formulating these various supplementary feedings, the cost of the supplementary feedings must be remembered if the patient has limited means.

SUMMARY

A case of massive resection of the small bowel, leaving only 5 inches (13 cm.) of jejunum and 10 inches (26 cm.) of ileum has been presented. A discussion of the dietary problems is presented and several formulas utilizing synthetic food stuffs are suggested. Emphasis has been placed on the importance of using synthetic food stuffs containing fat particles of small size as a dietary supplement.

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# DIFFERENTIAL DIAGNOSIS OF THORACIC TUMORS

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Thoracic tumors are difficult to diagnose because the clinical and roentgenologic findings can simulate any of the inflammatory lesions of the chest. The only way an accurate diagnosis of chest tumors can be made is by histologic identification of the cells. We believe that an accurate histologic diagnosis should be made before lung resection is done, even though some time may be sacrificed in exhausting all of the diagnostic methods. If pneumonectomy is done on the presumptive evidence of malignancy, there will be some patients who will have their lungs removed unnecessarily. The physiologic magnitude of the operation does not warrant such errors, even occasionally.

We will review the diagnostic procedures available and present cases which illustrate the varied clinical and roentgenologic pictures seen in some thoracic tumors.

## DIFFERENTIAL DIAGNOSIS OF CHEST TUMORS

The thought which must be kept in mind in interpreting an area of density in the chest roentgenogram is that any tumor can simulate an inflammatory process and any inflammatory process can simulate a tumor. The reason for this confusion is that tumors, by obstructing the bronchus produce inflammatory processes in the lung. The end result in either tumor or infection is atelectasis with pneumonitis. In most cases of bronchogenic carcinoma it is the pneumonitis which brings the patient to the doctor rather than the symptoms from the tumor itself.

Let us consider the course of events in a bronchogenic tumor. When the tumor first starts to grow in a bronchus it partially obstructs the bronchus. This partial obstruction may allow air to enter the lung beyond the lesion but makes it difficult for air to leave the partially obstructed segment. This phenomenon will lead to emphysema in the involved segment. As the obstruction becomes more complete, air no longer enters the segment so the segment becomes airless or atelectatic. Obstruction almost always results in infection so that the atelectasis becomes a pneumonitis. If the pneumonitis persists and the time interval is short, as in malignant tumor, lung abscess may result. If the obstruction persists and the time interval is longer, as in benign tumors, bronchiectasis may develop. If the pleura is involved, fluid will develop.

Therefore, when the patient first is seen he often complains of having a severe cold and is found to have cough, fever, leukocytosis and other evidence of respiratory infection. The roentgenogram looks like pneumonia, and the patient generally responds temporarily to treatment with antibiotics. In some of the

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peripherally located tumors the pneumonitis is more localized and is not such a prominent feature. These patients may show a definite tumor mass. If the peripheral lesions are seen early, they present as symptomless round shadows which are indistinguishable from tuberculomas in the roentgenogram.

For these reasons, the early diagnosis of carcinoma of the lung, which is so important if cures are to be obtained, is very difficult. The only criteria which can be laid down is to suspect any patient with a cough, hemoptysis, chest pain or wheeze, or any patient with a round lesion in the lung of having carcinoma. The more specific diagnostic methods that are available should then be used.

## DIAGNOSTIC METHODS

*History.* The four cardinal symptoms of carcinoma of the lung are cough, hemoptysis, chest pain and wheeze. One or all four may be present. The most important part of the history is to obtain accurate information regarding other conditions that might simulate carcinoma, such as a history of tuberculosis, aspiration of a foreign body, and asthma, always bearing in mind that carcinoma also may be present.

*Physical examination.* Much can be gained by careful physical examination, paying particular attention to evidence of enlarged cervical or axillary lymph nodes; paralysis of a vocal cord; paralysis of the diaphragm; evidence of obstruction to the superior vena cava; evidence of consolidation of the lung or fluid in the chest, and neurologic changes.

*Laboratory findings.* The routine laboratory tests often can give a clue to the diagnosis. Such tests as routine blood count, sedimentation rate, tuberculin reaction, Wasserman and coccidioiden tests should be done on every patient.

*Roentgenogram.* The roentgenogram is of course the main diagnostic aid in the study of chest tumors, if it is properly interpreted and properly correlated with clinical findings. In this connection a lateral roentgenogram always should be done. The first question to decide is whether the tumor is in the chest wall, mediastinum or lung. In some cases a small pneumothorax will help decide this point. If the tumor is located in the mediastinum, it is important to know whether it is at the hilus or in the anterior, posterior or superior mediastinum. Enlarged glands are generally hilar. Neurofibromas are generally posterior while teratomas are anterior. Aneurysms occur along the course of the aorta or pulmonary artery. If the disease is in the lung, the lobe or lobes involved should be determined, if possible, so that subsequent bronchoscopy will be more accurate. If the tumor shows as a round lesion in the lung, the differential diagnosis from tuberculoma may be difficult but in either case the lesion should be removed. When the tumor is a bronchogenic carcinoma and produces an area of atelectasis, pneumonitis, or abscess, further diagnostic methods must be pursued most vigorously, especially if it is in the upper lobe because of the similarity to tuberculosis. In some cases the roentgenogram shows evidence of fluid in the chest which should then be aspirated. In early carcinoma a localized area of emphysema may be the only evidence.

Fluoroscopy is an additional valuable roentgenologic procedure. It will show

pulsations of a tumor; movements of the lesion; position and movements of the diaphragm; and with a swallow of barium will often help to localize the tumor in relation to the esophagus.

*Bronchography.* In most cases bronchography is not very helpful in the diagnosis of bronchogenic carcinoma. Bronchography has two disadvantages. One is that the oil stays in the lung and makes future interpretation of chest roentgenograms difficult. Another disadvantage is that after instilling lipiodol, it is better to postpone operation for two or three weeks. However, in some cases a small quantity of lipiodol instilled only in the involved portion of the lung will be very helpful in that it may show the area of obstruction.

Planograms may be useful to show a tumor in a major bronchus but in our experience they have not been very helpful.

*Bronchoscopy.* Bronchoscopy is the most useful procedure we have in diagnosing endobronchial lesions. If the tumor can be seen and tissue for biopsy taken, the diagnosis can be made with certainty. Unfortunately, there are about 40 per cent of cases in which the tumor is so located as to be inaccessible to bronchoscopic vision. However, bronchoscopy has other values. The diagnosis of other lesions as tuberculosis or foreign bodies can be made in some cases, thus ruling out carcinoma. Widening of the carina may be evidence of mediastinal gland involvement. Bronchoscopy may hasten the resolution of a pneumonitis not due to malignancy. Every patient who is suspected of having malignancy of the lung should have a bronchoscopic examination done.

*Sputum Stains.* More recently interest has been directed to identification of cells which are exfoliated from endobronchial malignancies. These exfoliated cells may be identified in the sputum or in bronchial washings. Benign or metastatic tumors generally do not exfoliate. The method has been very helpful to us and should be part of the diagnostic procedures in every case of suspected malignancy when bronchoscopy does not reveal the tumor.

A very good method is to grasp a small piece of gelfoam on a forceps and wipe the suspected area of the bronchus. The entire gelfoam sponge can be sectioned. Often malignant cells will be caught in the meshes of the sponge and can be identified in the sections.

*Aspiration Biopsy.* Another method of diagnosing malignancy is to do an aspiration biopsy. If there is pleural fluid, cells may be found in the fluid. In other cases a needle may be inserted into the tumor itself to obtain malignant tissue. The trouble is that in most cases the tumor itself is much smaller than the accompanying pneumonitis, and the needle biopsy is not often successful in making the diagnosis.

*Evidence of Metastasis.* Many lung cancers metastasize very early. The metastases commonly are found in lymph nodes, brain, opposite lung, liver or adrenal. These metastatic lesions should be carefully searched for and recognized before operation is undertaken.

In suspected cases as a diagnostic procedure the fat pad over the anterior scalene muscle should be removed. This fat pad always contains lymph glands. Often glands as small as 3 mm. in diameter show malignant cells. Unfortunately,

the spread to those glands occurs early. Finding malignant cells in these glands will not only help in establishing the diagnosis but will establish the presence of early metastasis.

The advisability of palliative pneumonectomy for carcinoma of the lung with known irremovable metastasis depends upon the philosophy of the surgeon and the individual patient.

*Exploratory Thoracotomy.* When all of the diagnostic methods have been exhausted, exploratory thoracotomy should be resorted to. Much is being written and said about the safety of exploratory thoracotomy. However, we do not believe that exploratory thoracotomy should be rushed into or abused. Twenty years ago it was not uncommon to see two or three exploratory laparotomies scheduled in a single morning in a large hospital. Now you rarely see an abdomen opened without a diagnosis having been made. A diagnosis should be made before the chest is opened if possible. However, it is sometimes difficult to make the diagnosis with the chest open because the inflammatory process obscures the malignancy.

We believe that the operation of pneumonectomy is of such physiologic magnitude and the number of cancer cures so few that a total pneumonectomy should never be done on a *presumptive* diagnosis of cancer. A lobectomy may be justified, provided the alternative diagnosis would warrant a lobectomy. Exploratory thoracotomy is safe and a valuable procedure provided all of the available diagnostic procedures have been thoroughly exhausted first. The lung should not be removed without an accurate histologic diagnosis. If you remove an appendix that is not diseased, you can justify the operation on the grounds that the patient is better off without his appendix, but no one can argue that a patient is better off with one lung than with two.

We have selected a group of patients to illustrate the diagnostic problems involved in various types of chest tumors. Chest tumors can be roughly divided into chest wall tumors, mediastinal tumors and lung tumors.

*Chest Wall Tumors.* Chest wall tumors are liable to involve intercostal nerves. Therefore, the first symptom will be pain. If the tumor is located low enough to involve intercostal nerves which distribute to the abdomen, the first symptom may be abdominal pain. Gallbladder disease may be suspected in some patients. If there is no nerve involvement, the tumor may reach huge size before it is suspected. Of the nonmalignant tumors the most common are osteochondroma and myxochondroma. These tumors are not malignant initially, but may become malignant.

Case I. M. W., a 19 year old girl, complained of pain in the upper abdomen. Roentgenogram showed an expanding tumor of the rib in the region of the costochondral junction (fig. 1). The tumor was removed. It was found to be an osteochondroma. There has been no recurrence in 14 years.

*Mediastinal Tumors.* It is important in suspected mediastinal tumors to have a lateral chest roentgenogram. The position of a mediastinal tumor with relation to the anterior or posterior chest wall is important. Neurofibromas are generally

posterior while teratomas and thymomas are anterior. Tumors around the hilus are generally enlarged glands from tuberculosis or lymphoblastoma. Fluoroscopy will help to identify pulsation if the tumor is in relation to the aorta. A swallow of barium while the patient is receiving fluoroscopy will help to locate the relation of the tumor to the esophagus.

Case II. Mrs. S., 42 years old, complained of pain in the left upper abdomen. Postero-anterior roentgenogram showed a shadow which appeared to be continuous with the cardiac shadow. On lateral roentgenogram the tumor was found to be posteriorly located (fig. 2). The tumor was removed and proved to be a neurofibroma.

Case III. B. T., a 4 year old boy, gave a history of fever of three weeks' duration. Roentgenogram showed a tumor in the left chest which on lateral roentgenogram was seen to be in the anterior mediastinum (fig. 3). At operation a malignant tumor was found. The diagnosis was malignant teratoma. The child died in about nine months.

Case IV. H. S., a 30 year old woman, had had occasional pain in the anterior chest. Routine roentgenogram showed a mediastinal mass (fig. 4). Because the diagnosis was obscure, thoracotomy was done which showed encapsulated lymph nodes. Cultures and guinea pig inoculation of the caseous material from the nodes were negative for tubercle bacilli. However, the nodes were tuberculous in origin. Samson has contended that tuberculous lymph nodes should be removed because of the difficulty in making the diagnosis.

Case V. J. J., a 54 year old woman, had complained of severe cough. Roentgenograms were thought to show mediastinal lymphoblastoma and a full course of roentgen therapy was given without decrease in the mediastinal shadow (fig. 5). A positive Wasserman reaction lead to suspicion of aneurysm, and pulsation of the tumor on fluoroscopy confirmed the diagnosis. The aneurysm of the ascending aorta was wrapped with cellophane. The operation was followed by considerable relief of symptoms.

Substernal goiter must always be considered in the diagnosis of superior mediastinal tumors.

*Intrapulmonary Tumors.* Intrapulmonary tumors may be benign or malignant. The benign tumors may be intrabronchial or extrabronchial. If the tumor is intrabronchial it produces a wedge-shaped area of atelectasis. Because of the long standing obstruction, bronchiectasis commonly is associated. *Benign* bronchogenic adenomas are prone to bleed profusely, but the hemoptysis generally ends abruptly. On the other hand, malignant tumors bleed continuously but not profusely. The course is rapid in carcinoma so that the inflammatory reaction leads to pneumonitis or abscess.

*Benign Bronchogenic Tumors.*

Case VI. I. C., a 20 year old girl, gave the history of having had pneumonia at the age of 12, followed by a persistent cough with repeated respiratory infections. She had foul sputum. Hemoptysis had occurred on three occasions. Roentgenogram showed an atelectatic right lower lobe (fig. 6). The patient was thought to have bronchiectasis. Bronchoscopy revealed an adenoma of the right main bronchus. A pneumonectomy was done. The patient has been well and has had two children since the operation. This patient with symptoms

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FIG. 1. M. W. Osteochondroma.
FIG. 2. Mrs. S. Neurifibroma.
FIG. 3. B. T. Malignant teratoma.
FIG. 4. H. S. Tuberculous lymph nodes.

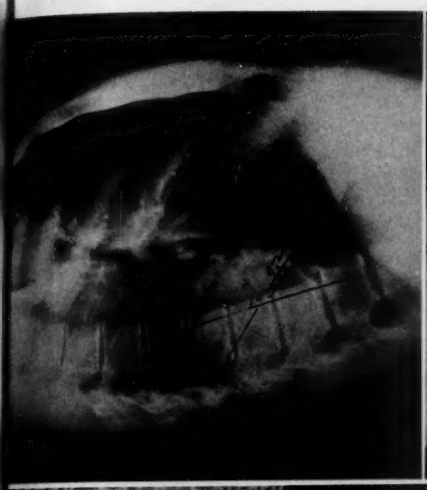

Fig. 2

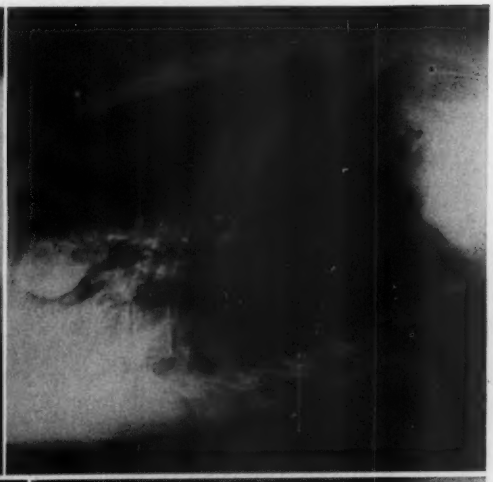

Fig. 4

Fig. 1

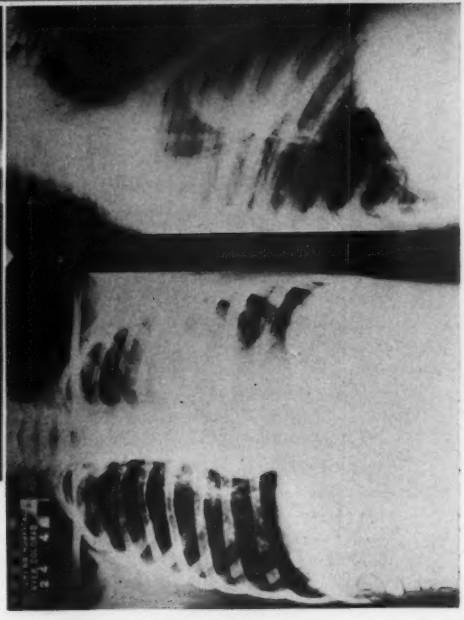

Fig. 3

of many years duration now shows lymph node metastases six years following pneumonectomy.

These so-called *adenomas* do metastasize to lymph nodes and by the blood stream although they do so over a protracted period of time.

Case VII. D. B., a 54 year old man, on routine chest roentgenogram (fig. 7) was found to have a tumor in the lung. Bronchoscopy was negative. At operation, a hamartoma was found arising from the left upper lobe bronchus. There has been no recurrence following removal. These tumors are benign and can produce obstructive symptoms and hemoptysis.

*Bronchogenic Carcinoma.* The group of patients we will show with bronchogenic carcinoma illustrate the difficulties in diagnosis. In all of the cases the diagnosis was made from the roentgenogram which had to be revised subsequently. There seems to be some tendency among clinicians to believe that the diagnosis should be made from roentgenograms of the chest. Also there is a tendency to criticize the roentgenologist who fails to make a diagnosis from the roentgenogram alone. As a matter of fact, a diagnosis of carcinoma of the lung from the roentgenogram alone is no more accurate than a diagnosis of appendicitis from leukocytosis alone. The roentgenogram often only shows an area of atelectasis and pneumonitis.

The first group of cases illustrate carcinoma which simulated pneumonia in the roentgenogram because of the associated obstructive pneumonitis.

Case VIII. J. C., a 42 year old man, is interesting because of the sequence of the roentgenograms. The patient had a respiratory infection for which he was hospitalized. Roentgenogram showed an area of increased density at the left base (fig. 8). He was given penicillin. Roentgenogram one week later showed definite clearing (fig. 9). He was discharged as cured. However, he began to streak blood and two weeks after discharge from the hospital he was readmitted. Diagnosis of oat cell carcinoma was made from bronchoscopic biopsy section. At operation, the lesion was too far advanced to be operable. It is almost impossible to get cases of undifferentiated oat cell carcinoma early enough to hope for cure.

Case IX. F. B., a 54 year old man, gave a history of a cough of three months' duration. He was working in a chemical plant. He had fever of 102 F. and the roentgenogram appeared compatible with pneumonia (fig. 10). Bronchoscopy showed undifferentiated bronchogenic carcinoma.

Case X. Mrs. C., a 64 year old woman, said her health had broken down five years previously. She was in bed for three months as a result of this illness. She has felt well since. A roentgenogram, at the time of the mass roentgenographic survey, was interpreted as miliary tuberculosis (fig. 11). The diagnosis of carcinoma was made by stains of exfoliated cells in the sputum.

Carcinoma with pleural involvement may form fluid in the chest. In these patients, thoracentesis often will help make the diagnosis.

Case XI. Mr. McE., a 54 year old man, said he had had a recent respiratory infection with persistent pain in the chest. Tuberculin test was positive. Lateral roentgenogram showed what appeared to be interlobar effusion (fig. 12). Lipiodol showed a block of the lingular division of the left upper lobe. At operation an oat cell carcinoma was found.

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FIG. 5. J. J. Aneurysm of the ascending aorta.
FIG. 6. I. C. Adenoma right main bronchus.
FIG. 7. D. B. Hamartoma, left upper lobe bronchus.
FIG. 8. J. F. *Pneumonia*—undifferentiated carcinoma with obstructive pneumonitis.

Fig. 6



Fig. 5



Fig. 8



Fig. 7

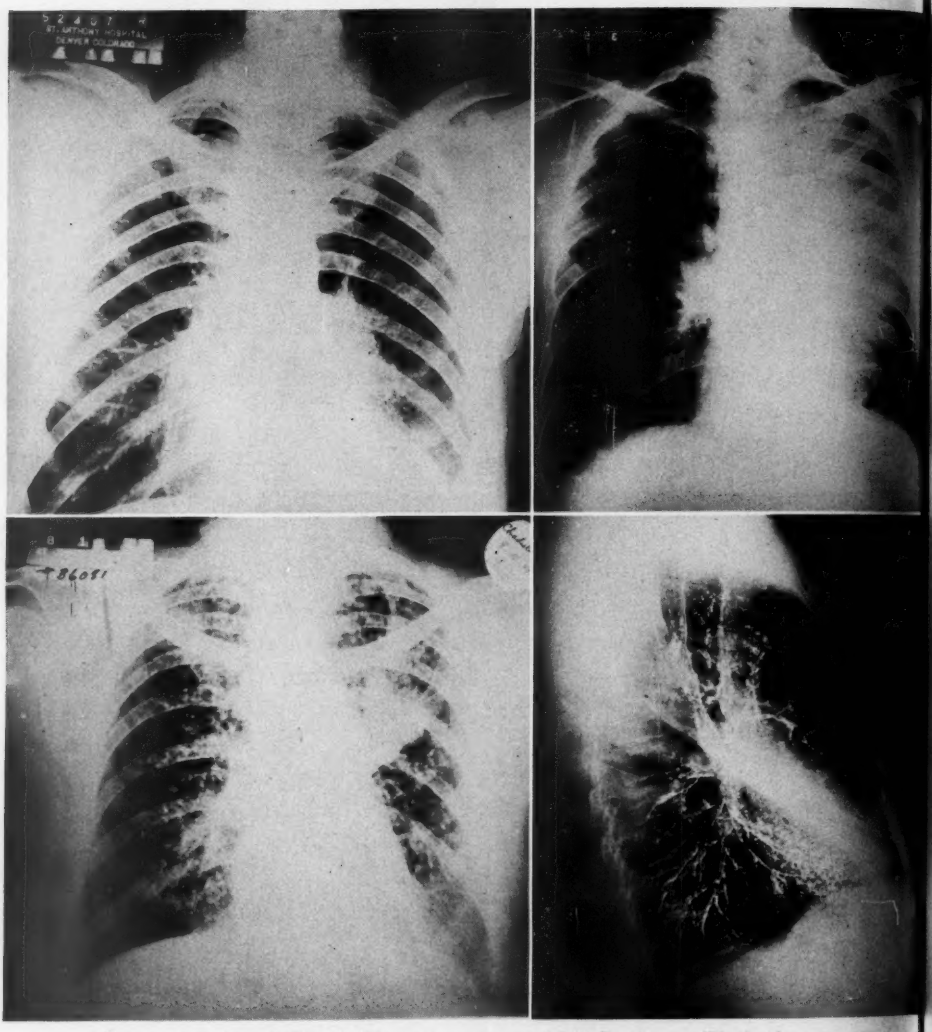

FIG. 9. J. C. Resolution of obstructive pneumonitis following antibiotic therapy—undifferentiated carcinoma.

FIG. 10. F. B. Obstructive pneumonitis secondary to undifferentiated bronchogenic carcinoma.

FIG. 11. Mrs. C. Carcinoma of the lung diagnosed as miliary tuberculosis.

FIG. 12. Mr. McE. Oat cell carcinoma of lingular division of left upper lobe simulating an interlobular effusion.

Round lesions should be explored. They are continuously seen in routine roentgenograms of the chest. They are frequently tuberculomas, but the diagnosis cannot be made without thoracotomy and removal of the round lesion for diagnosis.

FIG. 13



FIG. 14

FIG. 13. Mrs. G. Adenocarcinoma of lung thought to be a tuberculoma (1949).
FIG. 14. Mrs. G. Adenocarcinoma of lung thought to be a tuberculoma two years later (1951).

Case XII. Mrs. G., a 62 year old woman, had had a small round lesion for two years as shown by roentgenograms. It was thought to be a tuberculoma (fig. 13—1949). Exploratory thoracotomy showed it to be an adenocarcinoma (fig. 14—1951).

## CONCLUSIONS

The diagnosis of chest tumors may be difficult and confusing because chest tumors can simulate any of the inflammatory chest lesions. Lung carcinomas do, in fact, set up inflammatory processes in the lung. Before operating upon a patient with suspected carcinoma of the lung, every diagnostic method available should be used in an effort to make an accurate histologic diagnosis. The removal of a lung when pneumonectomy was not indicated is a major tragedy.

# FLAT SURFACE SKIN GRAFTING IN THE GENERAL HOSPITAL*

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Skin grafting is one of the principal technical procedures in reconstructive surgery. General surgeons have occasions for its use; neurosurgeons and orthopedists encounter problems where skin covering is deficient or inadequate; ophthalmologists, oral surgeons, and otologists occasionally face the need of cavity lining or resurfacing; reconstructive surgery requires skin grafting in all of its types and variations. Most three dimensional reconstructions and restorations fall within the scope of the latter specialty, but flat surface grafting properly belongs at times in other departments when they are equipped to do it well.

Use of the split skin graft for early healing of third degree burns; closure of traumatic wounds presenting full thickness loss of skin; and as a temporary expedient in preventing sepsis and minimizing fibrosis when deep structures are exposed, should be part of the training of all surgeons whose future responsibilities will include skin replacement. A denuded surface literally begs for cutaneous covering—and no other dressing upon a clean surface can compare with skin. Sepsis is thereby controlled and then obliterated; fibrosis is retarded and then stopped. No clean wound need become infected; no burn should remain long unhealed after necrotic tissue has separated; and no surface should stand denuded after excision of superficial tumors when integument is necessarily removed with the specimen. Thus, this paper is dedicated to the proposition that all wounds, including burns, should be closed at the earliest possible time.

Split skin is the most utilitarian of the several types of graft. It is often used as a temporary dressing even when later it is to be replaced by a pedicled flap or a thicker free graft. Heavier grafts finally will provide more substantial covering upon weight-bearing areas or over mobile structures, and their appearance is superior. Small deep, Reverdin, or pinch grafts are outmoded, for they cannot do anything that a split skin graft in one or another of its forms cannot do better—and without permanently harming or disfiguring a donor site.

No attempt will be made here to mention and discuss all uses of the split skin graft. We will review the most usual indications for skin replacement with partial or split thickness grafts, with emphasis upon technical steps upon which success depends and in the absence of which failure is invited.

## INDICATIONS

*Burns:* Depth of a burn is determined the moment it happens, but accurate diagnosis of the extent of full thickness necrosis usually will not be known until its gray-green color and line of demarcation delineate it from the normal skin. Deep second degree burns rarely are converted into third degree burns by bac-

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terial destruction or by over-zealous application of escharotics, coagulants, or lytic agents. This complication has become less frequent with our broadened perception of burns as wounds, to be kept clean until first and second degree burns have healed spontaneously and third degree burns have been resurfaced surgically. It is not sensible to await spontaneous healing of wounds from their edges with scar and scar-epithelium of quality which deteriorates as it painfully and hesitatingly approaches the center. The border will become keratotic, finally surrounding a chronic ulcer which may never heal, or at best will heal and break down—a vicious circle which begets malignant changes. Such unfortunate events have become rare as availability of successful skin grafting has increased. Thus burn wounds larger than a few centimeters, which cannot heal within several days after necrotic tissue has demarcated and been trimmed away, should be prepared for surgery.

*Full thickness losses from trauma:* In war, in industry, and in an unstable and speed crazy populace human flesh is blown, slashed, scraped and torn away. Great wounds are made, and many cannot or should not be directly closed. Tension and tight sutures cause ischemic edges which are denied their circulation; resistance to infection is impaired, and the wound therefore cannot heal. Wounds need rest, elevation, gentle pressure, and a chance to heal. Meanwhile—after gentle white soap cleansing and physiologic sodium chloride solution irrigation, exploration, diagnosis, identification of structures, and debridement—there is no dressing superior to the thin or intermediate split skin graft. By its use there is much to gain and nothing to lose, for it prevents or minimizes sepsis and inhibits fibrosis. It will serve at least as a superior temporary dressing, even where later it must be replaced by a thicker free graft or a pedicled flap. When more elaborate definitive procedures are necessary or desirable for facilitating orthopedic or neurosurgical work, for improving permanence and durability on areas which must withstand trauma, or for improved appearance, early closure by the split skin graft will have immeasurably facilitated the work.

*For immediate closure of defects following excision of tumor:* Surgery of superficial tumors may demand sacrifice of skin to the extent that wound closure is impossible or undesirable because of tension. Again, there is no dressing superior to a split skin graft regardless of secondary and definitive procedures.

*Resurfacing areas of irradiation atrophy:* Fewer of these cases are seen now that roentgen rays are applied by qualified people; dangers of over-exposure are more generally known, and superior equipment and technic have evolved. However, old cases appear with intolerably sensitive and unstable scars, chronic ulcers, and malignant changes. It has been said that the relentless deterioration of these areas will always lead to cancer if the patient lives long enough. Nobody can disprove this statement, but ample evidence attests its foundation in fact. In many of these cases, subcutaneous structures are capable of nourishing a split skin graft. Ulcerated and atrophic tissues may be dissected away; edges allowed to retract, and the graft applied. Relief of discomfort is usually dramatic, and the patient is grateful also for improved appearance, freedom from repeated dressings and fear of cancer.

*Decubitus ulcers:* Every general hospital has perennial problems with pressure sores, which would be far more frequent except for awareness of our faithful nurses. Prophylaxis is, of course, the key to minimizing pressure necrosis. Aged, debilitated, and paralyzed patients cannot long withstand pressure upon any area. Several full thickness losses of skin have occurred across the lower dorsal surface of the neck where the band of an oxygen mask has pressed; moisture, fever, casts, braces, and transportation of patients are among many contributing factors. Personnel must be reminded by the staff and by each other to be ever mindful of the hazard of even slight neglect. Once necrosis has occurred, debridement, wet dressings and early skin grafting are indicated. Avascular structures, such as fascia, ligaments and bone may be exposed. In such cases, local rotation or sliding skin flaps are required, with split skin grafts to donor areas when defects are large. Closure under tension will beget failure. Bony prominences, such as the greater trochanter and ischial tuberosity, should be chiselled off before the flap is maneuvered into place. The cancellous bone constitutes a helpful source of blood supply to aid healing. Etiologic factors in pressure necrosis are ever present and can cause new sores upon the same old sites. Eternal vigilance always pays off!

## PREPARATION OF THE WOUND

When skin has been fatally burned or crushed, time is required for living and dead tissue to be delineated—one from the other. A rare exception is the not too extensive third or fourth degree burn from contact with a hot object which permits immediate diagnosis of its depth and extent. Circumstances may then permit prompt excision of the wound and application of a split skin graft at once. Electrical burns often are through and through the tissues and require time for diagnosis and debridement. Perception of burns as open wounds should be taught our students and maintained by all attendants. Gowns, gloves, and masks—including the patient if his wounds are in line with his own droplet contamination—should be used when dressings are changed. Aseptic precautions from the first dressing until wounds are healed minimize contamination and simplify the bacterial picture. Shock, fluid replacement, sensitivity tests and antibiotic therapy are beyond the scope of this paper. Medical consultation and laboratory assistance are of course enlisted—care being taken that all workers are interested in the burn problem, and that each is aware that the severely burned patient is dangerously sick, his life dependent upon faithful cooperation of those who attend him. Early closure of his wounds reverses the picture of a shocked, feverish, demoralized patient to one who works toward his own recovery, eats well, and smiles once again. Incidentally, we believe that ACTH is helpful during the stage of preparation, but may retard healing and *taking* of grafts when continued beyond that time.

Dressings should be changed often enough to preclude odors of decomposition. Foul soggy dressings beget fever, discomfort, demoralization, and toxic absorption. Removal of outer dressings and washing of uninvolved parts with soap and water may be followed by immersion of the extensively burned patient in a

tub of warm physiologic sodium chloride solution. He will then assist in removal of his dressings. Over use of narcotics is fraught with danger of addiction, and too frequent sedation and general anesthesia contribute to disastrous disturbance of the pain threshold. Sodium phenobarbital given hypodermically often serves as an adequate substitute for opiates. Inhalation of trilene is a boon and a blessing in facilitating removal of dressings and debridement of wounds, which as a rule best may be done about every two to four days until time for final preparation for operation. We may anticipate that surgery will be feasible within three to four weeks from the time of the accident.

Lytic substances, such as pyruvic acid and the streptokinase-streptodornase preparations, hasten separation and solution of necrotic tissue; local and systemic use of antibiotics are helpful in controlling unavoidable bacterial invasion. However, we believe that antiseptic precautions, frequent nonadherent dressings of ointment impregnated fine mesh gauze or silk or nylon cloth of one's choice, respect for patients' feelings, and early closure of wounds with split skin grafts are more important than any combination of so-called *recent* innovations. Open air treatment is not new, but has had a recent inning. In case of catastrophic burning of hundreds or thousands of people, it might become necessary for reasons of economy. However, most of us believe that dressings—as above—plus many hours of kind attention by interested doctors and nurses constitute the primary considerations in the management of burns.

Most principles of burn therapy apply to treatment of traumatic wounds where skin grafting is indicated. Some may be cleansed, debrided, and grafted at once. Others, as in crushing wounds, must await demarcation, separation of slough, gentle dressing, and appearance of granulation tissue. In either burns or delayed grafting of traumatic wounds, the immediate preoperative treatment usually consists of two or three days of dressings damp with physiologic sodium chloride solution, and fine mesh dry gauze applied next to the wound. In some cases, dressings are changed every six to eight hours during the last day before operation. Damp dressings are more absorbent than wet ones.

## TECHNIC

Since every granulating surface is contaminated with bacteria, it is wise to procure skin grafts with hands and instruments that are clean. Donor areas are shaved and prepared with soap and water, ether, and alcohol. When possible, donor areas are selected which need not bear weight and which can be readily immobilized with pressure dressings. Thighs, lower legs, abdominal wall, and the back usually are selected in this order. Amount of skin needed can be estimated with fair accuracy. Requirements to cover a large defect seem always to exceed a casual estimate.

Methods of cutting grafts vary with individual preference and experience. Many surgeons are skilled at free hand cutting, using the razor knife with or without the roller held a calibrated distance from the edge to prevent cutting too deep. The dermatome, with drum and glue, is still extensively used; however, it is time consuming and comparatively awkward. Electric machines with oscil-

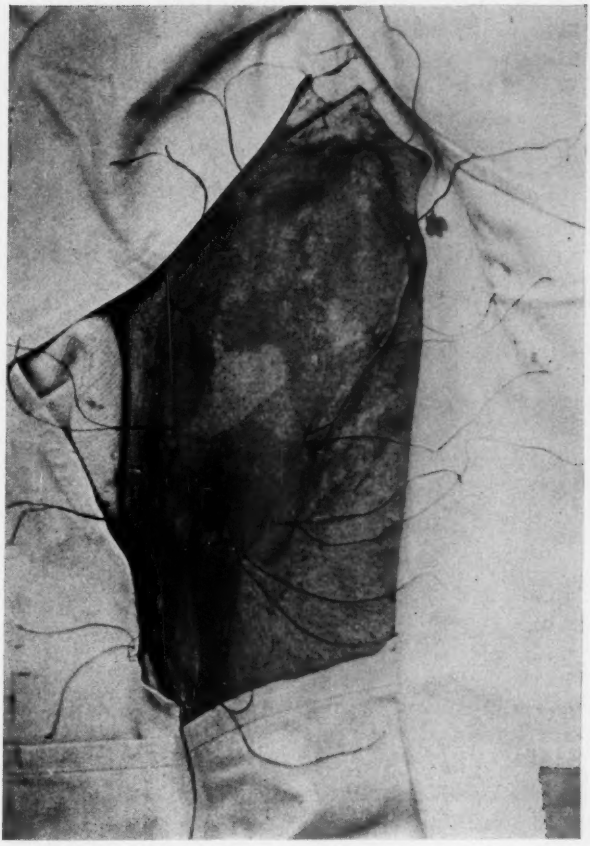

FIG. 1. Split skin graft *tacked* under tension of normal skin with silk sutures. End sutures are left long to tie across first layer of dressings.

lating blade work quickly and permit more surgery to be done within a reasonable operating period. An operation which will require more than two or three hours usually should be divided into stages. In such cases, hands, eyelids, and flexor surfaces of joints should be given priority, other areas to be grafted as soon as feasible. When grafts are cut reasonably thin, perhaps .010 to .012 inch, in thickness, donor areas may be used up to three or even four times at intervals of a few weeks when necessary. For economical utilization of skin in extensive burns with limited available donor skin, the latter may be cut into patches or stamps and distributed upon the recipient areas in order to start a maximum number of healing edges from which new epithelium will progress over the wounds. It seems trite to mention that the donor must be the patient himself, except in rare instances when an identical twin is available. Skin from other donors serves only

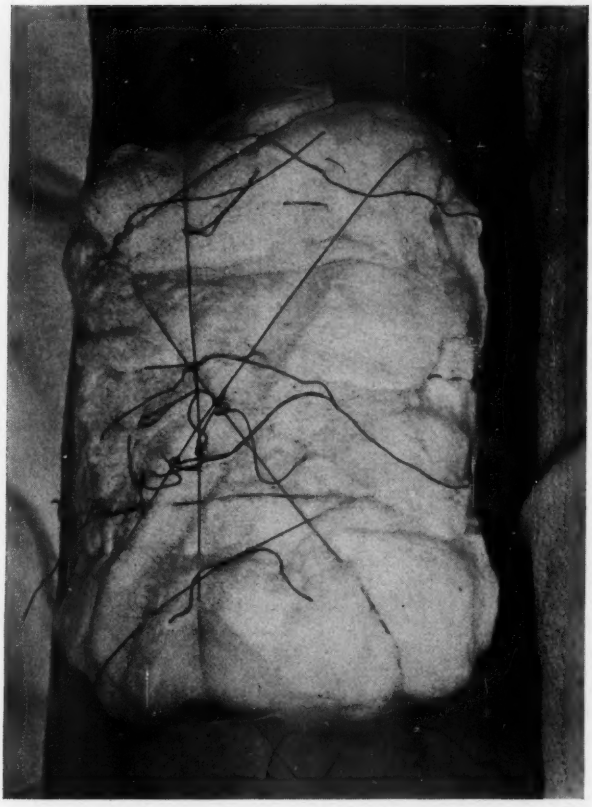

FIG. 2. Silk stitches, tied across dressings like a package, assure perfect immobilization and pressure.

as a temporary dressing until separation and loss of such grafts occurs within three to eight weeks.

Quality and depth of granulation tissue varies; it may be thick, slushy and pale, or it may be flat, red and firm. It is advisable in either case, to freshen its surface by sharp dissection—not by scraping, rubbing, or tearing. Innumerable open capillaries will bleed freely, but physiologic sodium chloride solution packs and pressure will minimize the fluid loss. The capillary vessels will grow rapidly into the grafts, which are secured in place and gentle but firm pressure applied.

Except in the most extensive wounds, all of the granulation tissue may be covered with grafts. Wounds up to 4 by 8 inches may be covered by a single sheet of split skin; even larger wounds are occasionally covered by a skillfully cut free hand graft. It should be applied when possible under the tension of normal skin; i.e., a given graft will cover an area the size of its donor site (fig. 1). Absolute immobility is mandatory and may be assured by silk or cotton stitches

FIG. 3. Too-thick graft nearly totally lost.

about the border of the graft. This is especially desirable on areas where circumferential pressure is difficult to apply and maintain. Suture ends may be left long and tied criss-cross over the first layer of dressings which is composed of fine-mesh petrolatum gauze—not too greasy—and pads of gauze, cotton, or waste (fig. 2). Elastic, bias-cut stockingette, curlex, or crepe bandages assure gentle uniform pressure. Light plaster dressings over these, when extremities are involved, will prevent flexion of joints.

Donor areas are dressed with petrolatum or scarlet red fine-mesh gauze and pressure dressings, left undisturbed usually for 10 to 14 days and removed when the areas are healed and pain and bleeding do not occur.

Though the initial dressing may be done on the third to tenth postoperative day, we believe that the optimum time is the fifth or sixth day. At that time stitches are removed, edges are trimmed and, blebs, hematomas, and pustules are slit open and contents expressed. Skin over blebs containing serum or blood

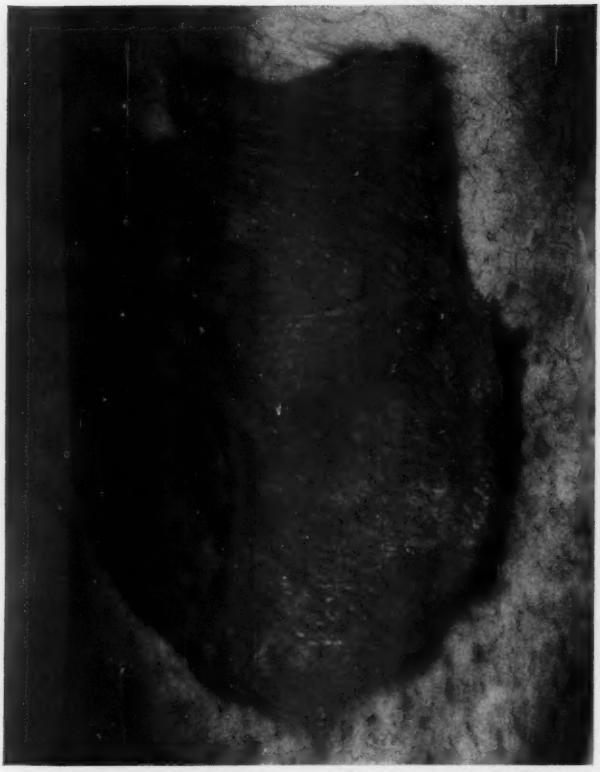

FIG. 4. Same area regrafted, with complete success, using a thin graft.

remains viable and will usually *take* after pressure is reapplied. Dressings are repeated every three to six days. Pressure should be continued carefully over each fresh dressing for at least three weeks. Rehabilitation is supervised, especially in burns of the lower extremities. In these cases, elastic bandages or stockings are suggested for three months or more.

Helpful observations and constructive technical criticisms may be made at the time of dressings. One of the commonest faults of the dermatome is the cutting of grafts which are too thick. Figure 3 shows a wound about 4 by 7 inches in size on a thigh which had been grafted with skin .016 or .018 of an inch thick. The graft failed to be nourished and attached and has been trimmed away except for a narrow border. This wound was promptly reprepared with physiologic sodium chloride solution damp dressings and regrafted with skin about .012 of an inch thick. Figure 4 shows complete *take* of the thinner graft.

The evils of too-thick grafts upon unhealed wounds cannot be over-emphasized. Figure 5 shows a donor area approximately 4 by 8 inches in size on a buttock which caused the patient far more grief than did the wound the graft was de-

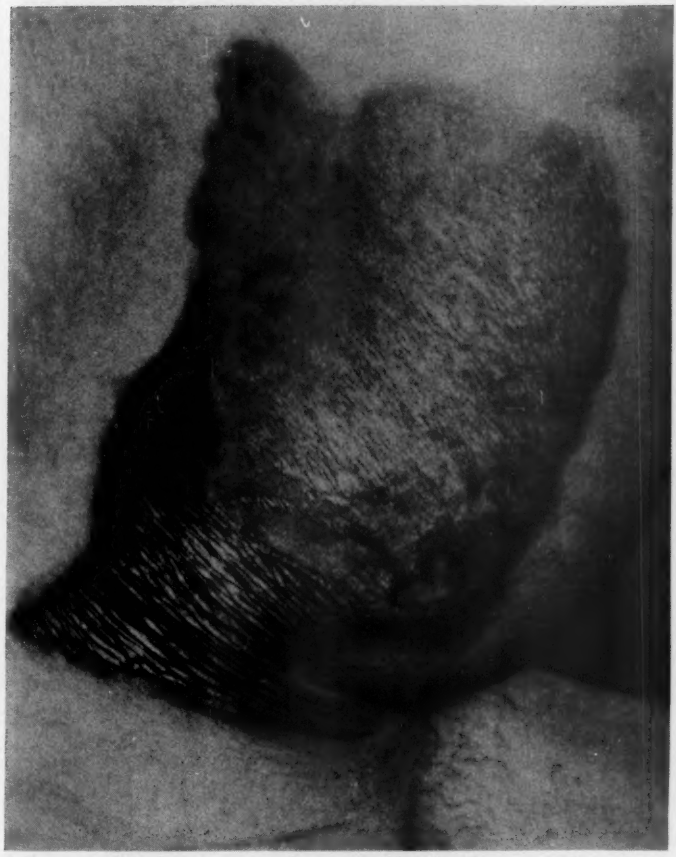

FIG. 5. Inappropriate donor area; graft was too thick; healing was prolonged and resulted in hypertrophied scar which was sensitive and itching.

signed to heal. These defects are peculiarly slow to heal, sensitive, and susceptible to infection; they usually result in hypertrophied scars which itch and burn indefinitely. Another error is depicted here. Immobility and pressure are nearly as essential at the donor area as upon the grafted wound. Dressings must not slide and irritate the denuded corium. The buttocks cannot be immobilized (fig. 5).

Tissues which have been crushed are usually more hurt than they at first appear to be. Injuries thought to be merely bruises may result in full thickness loss of skin, fibrotic muscles, thrombosed vessels, and contused and avulsed nerve trunks. The prognosis should be carefully guarded for a week to 10 days until the diagnosis is clear. Figure 6 shows such a wound, a typical wringer injury in a child. Lines of demarcation were present in a week, and full thickness slough

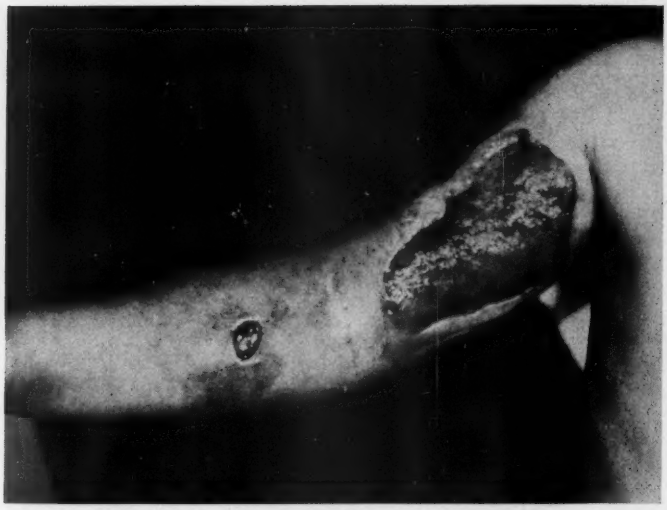

FIG. 6. Wringer injury with full thickness loss of skin, deep fibrosis of muscles, and avulsion of subcutaneous tissues from fascia.

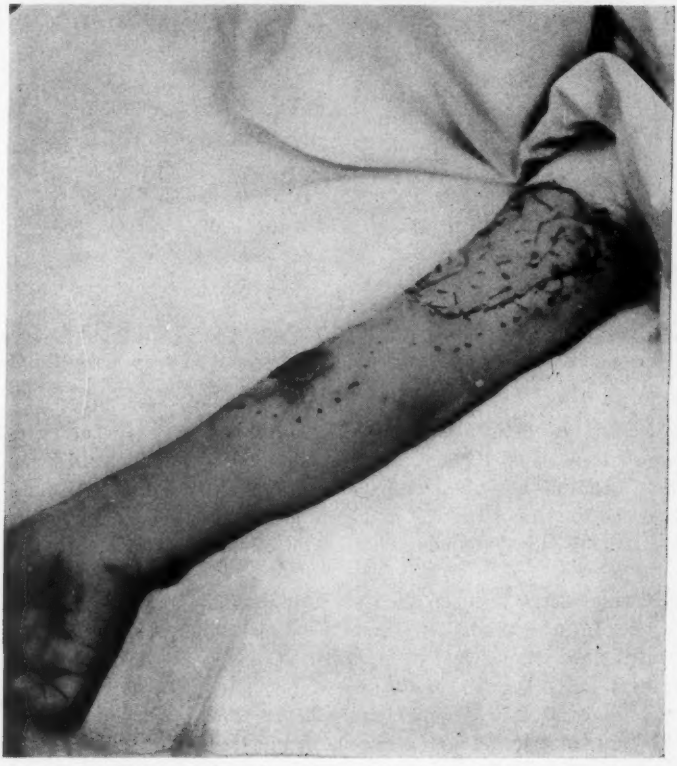

FIG. 7. Split skin graft sutured in place. Dotted line indicates extent of undercut edges.

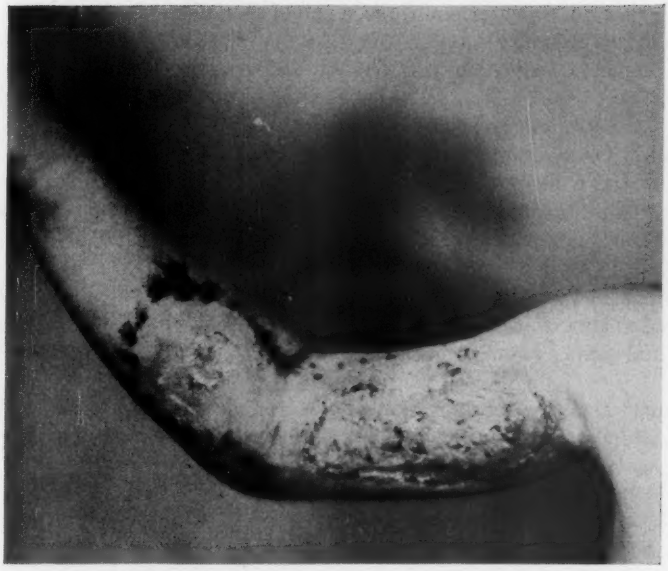

FIG. 8. Complete healing on eighth postoperative day, at time of second dressing. Protective pressure dressings should be maintained for another three weeks or longer until the graft and scar have matured.

was debrided away within another week; clean granulation tissue was ready for a split skin graft at the end of three weeks.

Edges of crushed wounds are often undercut or torn away from the underlying fascia. These *gutters* harbor necrotic tissue and purulent exudates and must be explored and cleaned at each preoperative dressing. Figure 7 shows the immediate postoperative condition, with single split skin grafts from thigh sutured in place. Since circumferential bandages about an extremity serve the purpose of immobilization so admirably, these grafts were basted on with continuous stitches rather than *tacked* with interrupted stitches. The dotted lines indicate the extent of detachment of skin and subcutaneous tissue from the fascia. Gentle pressure is, of course, essential to accomplish attachment of these tissues and to obliterate the dead space, as well as to facilitate ingress of new capillaries into the grafts.

The early postoperative condition is shown in figure 8. The wound was healed on the eighth day. The stitches are out, and blebs and small hematomas have been slit open and contents expressed. Gentle pressure is mandatory for at least another three weeks while grafts and fibrous tissue beneath it and about its edge mature.

## SUMMARY

The split skin graft is the most generally useful of all skin grafts. A working knowledge of its application and the factors upon which success depends should

be the property of every general surgeon and of specialists who face the responsibilities of open wounds.

Most common indications for flat surface grafting are discussed—burns, traumatic skin losses, closure following excision of superficial tumors, irradiation atrophy or ulceration, and pressure sores.

Technical points upon which successful flat surface grafting depends are discussed, and two illustrations are presented to emphasize a leading technical error—the too-thick graft, which ruins a donor area, causes the patient unnecessary suffering, prolongs healing, and requires repetition of all or part of the surgery.

Prognosis in burns and crushing injuries should be guarded until lines of demarcation appear and a definite diagnosis can be made.

Essential points in preparation, operation, and postoperative care are discussed.

Adequate time for rehabilitation of the wounded areas is mandatory, and protective dressings are particularly indicated for a few weeks or months upon the lower extremities.

# CLINICAL IMPLICATIONS OF THE METABOLIC RESPONSE OF THE BODY TO INJURY

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Within the past few years there have been numerous articles in the medical literature concerning various isolated aspects of the metabolic response of the body to stress and trauma. As physicians responsible for the supervision of patients under stress, because of illness or operation, we can best serve our patients by understanding the alterations in metabolism that characterize this state. The purpose of this communication is to summarize the more important of these metabolic changes and to indicate the clinical implications of this relatively new body of fundamental knowledge.

## ETIOLOGIC FACTORS

Adrenal release from the suprarenal medulla has been recognized as an important immediate reaction to trauma since the classical work of Cannon.[3] This immediate hormonal release is under sympathetic nerve control and supplies a quick but short-lived mobilization of body resources to combat the stress.[21]

Adrenal cortical hormones, on the other hand, under the trophic influence of the hypothalamus and the anterior pituitary gland cause metabolic changes that prepare the body for a more prolonged reaction to stress.[14] Three groups of adrenal cortical hormones are released under the trophic influence of ACTH, each having its characteristic metabolic effect.

1. The eleven-desoxycorticosterone group primarily effects salt and water metabolism, resulting in sodium retention and potassium excretion. Desoxycorticosterone acetate (DOCA) is a commercially available source of this hormone fraction.

2. The eleven-oxycorticoids primarily control protein catabolism, resulting in protein destruction in muscle and lymph tissue and in the disappearance of circulating eosinophils. Because of the relative facility with which the eosinophils in the circulating blood may be observed, this response is used as a convenient guide to the level of adrenal cortical hormone activity.

3. The third group of hormones released by the adrenal cortex are the 17-ketosteroids which have relatively little metabolic activity and are primarily concerned with the development of sex characteristics.[27]

*Chronology of Adrenal Hormone Response Following Trauma.* The etiologic importance of the adrenal hormones in the metabolic response of the body to trauma is emphasized by the correlation of the circulating concentrations of these hormones with the deranged metabolic activities which are known to result from such endocrine stimulation and to be characteristic of the postoperative and post-traumatic state.[24]

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Adrenalin and non-adrenalin release from the adrenal medulla is immediate but transient in the post-traumatic state. Within a few minutes the effect is gone.

The adrenal corticoids are secreted within an hour following stress and eosinophils disappear from the circulating blood to remain depressed for 3 to 7 days.[22] Depending on the degree of the trauma, corticoid activity, as measured by eosinopenia, may last from 24 hours to 7 days. This initial post-operative period has been termed by Moore the adrenergic-corticoid period.[18] He emphasizes that most of the metabolic changes characteristic of this phase can be accounted for on the basis of adrenal corticoid activity.

On about the fifth day following severe stress, the adrenal gland stops its abnormal activity and corticoid levels return to normal or abnormally low levels (the so-called corticoid withdrawal phase[18]). Eosinophil levels return to normal and soon to abnormally high levels, where they remain for 10 to 12 days until corticoid activity returns.

Following trauma, the seventeen ketosteroid excretion from the adrenal cortex is increased for a period of 24 to 48 hours; it then falls to subnormal levels, returning to normal values slowly over a period of 5 to 6 weeks. This prolonged depression of the seventeen-ketosteroids accounts for the depressed male libido and absence of menses in the female which may last for two months following major surgical procedures.

## THE IMMEDIATE RESPONSE TO STRESS

The immediate response to injury or stress is the release of adrenalin. All vital body reactions, such as those of the heart and brain, immediately are mobilized to peak efficiency while the less important organs, such as the intestinal tract, stop their function and become relatively ischemic.[6] The heart rate increases; the pulse pressure is narrowed; and peripheral vasoconstriction results in a blanching of the skin. A quick burst of energy results from the breakdown of liver glycogen and the release of glucose. If the entire 400 Gr. of available carbohydrate stores are utilized, a maximum of 1600 calories may be made available. This source of energy is soon dissipated and the body metabolism must turn elsewhere for a source of energy.

## MOBILIZATION OF THE LONG-TERM ENERGY RESERVES

*Fat Metabolism.* When the carbohydrate reserves are consumed, the body turns to its more distant energy depots, namely, to the fat stores. Gram for gram, fat contains more than twice the caloric value (9 Cal./Gr.) than carbohydrate or protein (4 Cal./Gr.). There are as well many kilograms of fat compared to the relatively few grams of available carbohydrate, so that many times the caloric value is available in fat depots compared to carbohydrate sources. In the 3 to 5 days following a major operation, a normal size individual may lose 2½ to 3 Kg. in body weight. About one-half of this total weight loss is due to fat destruction which amounts to ¼ Kg. of fat per day. This in turn represents about 2,250 calories furnished daily by fat in the postoperative period which is about five times the rate at which fat is consumed during starvation alone. Obviously the

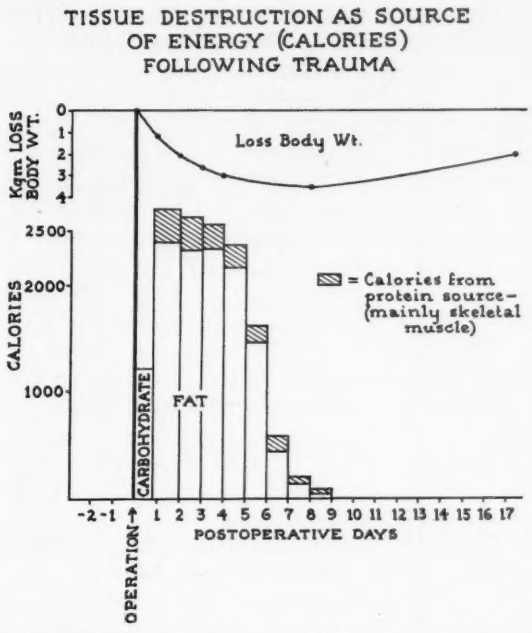



FIG. 1. Graph showing the normal loss in body weight following trauma and the source of calories consumed in the immediate postoperative period. Note the immediate and short-term function of carbohydrate as a caloric source as compared with that obtained from fat depots.

breakdown of fat following operation is caused not merely by lack of caloric intake, but is the result of abnormal fat catabolism.[8, 17, 18]

Under normal circumstances fat stores are catabolized at an abnormally high rate for a period of 5 to 7 days following operation. Abnormal caloric needs thereafter are largely furnished by protein breakdown (fig. 1). Weeks, and indeed months, may be required to return body weight to normal and fat stores as the least vital of the caloric depots are the last to be restored.

*Protein and Nitrogen Metabolism.* In 1928, Cuthbertson,[4, 5] while studying the metabolic response to long bone fracture, noted a marked negative nitrogen balance in all of his patients. This metabolic response has since been confirmed and reflects the marked protein catabolism that follows trauma and which occurs regardless of caloric or protein intake.[1, 2]

In the first 3 to 4 days following operation the individual may lose 15 Gr. of nitrogen per day. By the end of the third or fourth postoperative day this may amount to 1500 Gr. of protein, or 2.68 per cent of the total muscle tissue. This amount of protein will supply only 330 calories a day (17, 18) in contrast to the high caloric value of fat catabolized during this period. Protein catabolism during this period, in contradistinction to fat utilization, is at the same rate as would be found in uncomplicated starvation.[11]

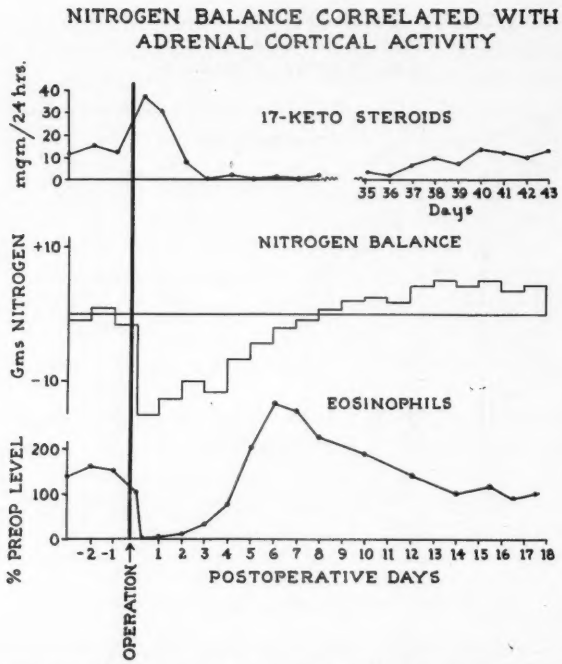



FIG. 2. Graph showing the correlation between the postoperative negative nitrogen balance and adrenal cortical activity, as measured by circulating eosinophils and 17-ketosteroid levels.

As circulating adrenal corticoids diminish on about the fifth postoperative day, the negative nitrogen balance decreases, signifying less protein destruction (fig. 2). About the seventh day, when the adrenal corticoids are normal or below normal, tissue repair begins and a positive nitrogen balance of about 3 to 5 Gr. per day is noted.[23] Such a positive balance continues for one or two weeks until the protein stores are restored—a condition that occurs weeks before the fat depots are refilled.

Recent studies from Korea[29] have shown that injured soldiers with acute renal shutdown maintained on the artificial kidney may show a marked negative nitrogen balance for many days or weeks following trauma. A number of such cases are cited where patients lose 30 to 40 pounds within a 3 to 4 week period. This loss is due almost entirely to extreme wasting of the peripheral muscle tissue. Such tissue depletion occurs despite a high caloric and high protein intake. Its cause and significance remain obscure.

Teleologically, there may be two reasons for the marked protein catabolism in the post-traumatic period. Protein may be converted to glucose and then metabolized as a source of energy (gluconeogenesis).[2] On the other hand, protein catabolism may be necessary to furnish protein for wound healing. In this regard

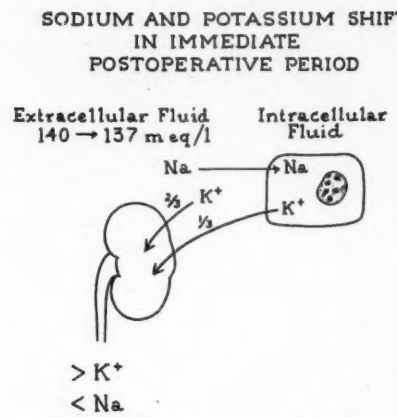
the body economy shows marked inefficiency for about 1800 Gr. of muscle tissue is destroyed in repairing a wound that in toto may require 20 Gr. of protein.[18]

*Clinical Implications.* During the past 15 years numerous attempts have been made to establish a positive nitrogen balance in patients in the immediate postoperative period. Efforts largely have been directed toward the intravenous and oral administration of protein and protein breakdown products (amino acids and protein hydrolysates). Others have attempted to diminish protein catabolism by the intravenous administration of large amounts of calories, either as carbohydrates or fats.[26] Experimental and clinical evidence indicates that intravenous caloric and protein intakes in amounts commonly used will not appreciably change the negative protein balance characteristic of the immediate postoperative period (2 to 5 days). The routine use of intravenous protein breakdown products during this period, therefore, appears to be a needless expense with little or no benefit to the body economy. Protein catabolism during this short time apparently results from hormonal stimulation and is not appreciably effected by intravenous or oral caloric intake. Corticoid withdrawal usually occurs on about the third to fifth postoperative day. At this time if the patient is given an adequate diet, protein again may be formed. By the fifth postoperative day most patients are taking food by mouth, so that only in the complicated case will parenteral protein actually be required. Due to ignorance of the metabolic effects of operation, and possibly to the persuasive effects of advertising, large amounts of parenteral protein are needlessly administered to many patients in the immediate postoperative period. Most of this protein is either destroyed as a source of calories or spilled in the urine as a manifestation of the negative nitrogen balance so characteristic of this state.

### SODIUM AND WATER METABOLISM IN THE POST-TRAUMATIC PERIOD

Immediately following trauma when the salt-regulating adrenal cortical hormones are being secreted in large amounts there is a marked diminution in the sodium excretion in the urine[5, 12, 15, 17, 18, 25] and in the sweat.[10] With this retention of sodium there is a concomitant oliguria. Fluid administered to these patients in excess of their urinary output is stored in the body as edema fluid and —far from being of value in stimulating diuresis—may be of serious detriment to the body economy. As the urinary volume decreases and the urinary sodium and chloride diminish, there is a somewhat paradoxical decrease in the plasma sodium concentration—paradoxical, that is, until one appreciates the fate of potassium during this time. The decreased plasma sodium level following trauma is explained by the movement of sodium from the extracellular space into the intracellular space, where it takes the place of the potassium which is flowing out of the cell and being excreted in large amounts in the urine (fig. 3). Because of this shift, the plasma sodium level may drop from approximately 140 mEq./L to about 137 mEq./L. This is a perfectly normal reaction and takes place in the face of minimal sodium loss in the urine.

On about the fourth postoperative day when the adrenal corticoids begin to decrease a reversal of the previous sodium and potassium shift takes place. A




*The effect of the adrenal 11-oxy corticoids in the immediate postoperative period resulting in 1) Sodium retention 2) Oliguria 3) Potassium excretion 4) Slight diminution in plasma sodium level 5) An increase in intracellular sodium and a concomitant decrease in intracellular potassium.*

FIG. 3

marked sodium and water diuresis occurs. Sodium pours out into the urine from both the intracellular and the extracellular space (fig. 4). If the physician has loaded large amounts of either sodium or water into the patient during the immediate postoperative period, the diuresis during the following corticoid withdrawal stage may assume alarming proportions. Paradoxically enough—unless one appreciates the potassium and sodium shift—the plasma sodium at this point will return to normal due, of course, to the egress of the sodium from within the cell into the extracellular space.

It is of passing clinical interest that the sodium and chloride concentrations in sweat during these periods of adjustment exactly parallel their concentration in plasma.[10]

By the end of the seventh to tenth day of an uncomplicated postoperative course when corticoid levels are below or near normal, sodium and potassium levels in the blood and urine are at preinjury levels.

Postoperative changes in water balance are not solely the result of adrenal corticoid activity. Such changes are also due to the shift of fluids from the intravascular to the interstitial space as a result of trauma and tissue damage.[19, 28] An obvious clinical example occurs in the swollen soft tissue of an injured extremity. In abdominal wounds, such swelling of the soft tissues may be less evident but is none the less important in causing a major change in water metabolism following trauma. By actual measurement several liters of water may be sequestered from the working body economy in such an area of swelling following tissue damage.

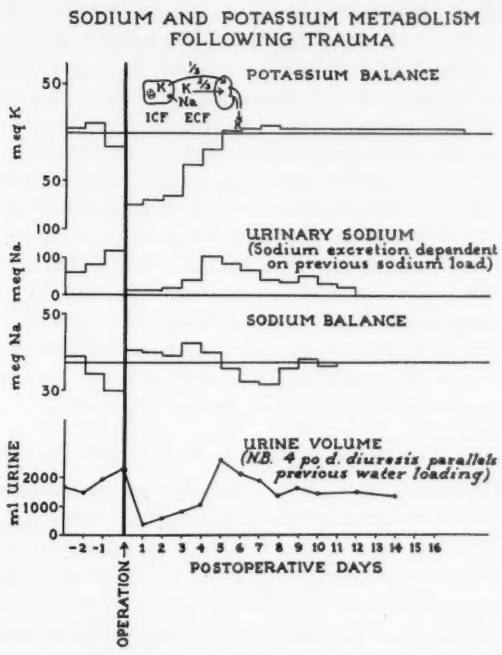



FIG. 4. Graph showing the sodium retention and the potassium diuresis that occurs in the immediate postoperative period. The diagrammatic insert schematically depicts the source of the potassium lost in the urine as being both from the normal plasma potassium and as a result of a potassium shift from within the cell. The bottom graph shows the postoperative oliguria which occurs simultaneously with sodium retention.

The obvious clinical implication of this internal shift of body water is to minimize tissue damage during surgery so as to minimize the amount of tissue edema. It is evident that the Halstedian surgical principle of gentleness in handling tissues has a firm metabolic basis.

*Clinical Implications.* The characteristics of sodium and water balance peculiar to the postoperative period are of major clinical importance to the physician who is responsible for furnishing these vital substances to a patient who is unable to take anything by mouth. To complicate matters, the patient often is unable forcibly to protest concerning his feelings of thirst or satiation, so that control of intake rests solely with the physician. The incompletely informed clinician, with sodium and chloride readily available as physiologic saline, often administers excessive amounts of these substances to a patient who cannot utilize them. Because of the sodium-retaining character of the body metabolism in the immediate postoperative period, parenterally administered sodium is largely stored in the interstitial space as edema fluid. This may be of danger in delaying wound healing, interfering with intestinal anastomoses or overloading the cardiovascular system.

A more acute danger of an excess loading of sodium and water in the immediate post-traumatic period is when this fluid is mobilized and returned to the intravascular space. On or about the fourth postoperative day when the eleven-desoxycorticoids decrease, water and sodium previously stored in the interstitial space suddenly return to the intravascular space and may result in disaster by causing an overloading of the cardiopulmonary system. Clinically, this is manifest as pulmonary edema and is seen in its most malignant form in severely burned patients who have mistakenly received large amounts of sodium in the fluids administered to overcome shock. Such patients suddenly may develop severe and even fatal pulmonary edema on the third to fifth postburn day just at a time when the clinician begins to think that his patient has a chance of survival. The clinical implication is clear—namely, that sodium should be given sparingly in the postoperative period, for salt loading at this time merely creates edema which upon its later mobilization may cause serious overloading of the cardiopulmonary system.

### POTASSIUM METABOLISM IN THE POST-TRAUMATIC STATE

Immediately following trauma when the adrenal corticoids are secreted in large amounts there is an increased loss of potassium in the urine, amounting on occasion to 70 mEq. per day. In the first three postoperative days, 6 to 7 per cent of the total body potassium thus may be excreted in the urine. After this period, as adrenal corticoids slowly decrease there is a decreasing potassium diuresis, until by the seventh to tenth day potassium may be restored to normal.

Two mechanisms might be operative in supplying the potassium lost by diuresis in the postoperative period. First, the potassium might be released following cell destruction; or second, potassium might flow out of the intact cell into the extracellular space and then into the urine. When cells are destroyed 2.7 mEq. of potassium are released for every gram of nitrogen. If this mechanism were the sole source of potassium, this ratio of potassium to nitrogen would be maintained in the urine. This is not the case, for in the postoperative period the urinary ratio of potassium to nitrogen is approximately 5 mEq. K/gm. N. This would indicate that about one-third of the excreted potassium arises from the intracellular fluid, where its place is temporarily taken by sodium.

As soon as potassium diuresis terminates—about the third to fifth day—a strongly positive potassium balance can be established, and by the end of seven days a normal balance may be established if sufficient potassium has been administered. It will be remembered that this is in contrast with nitrogen balance which despite the addition of protein will not return to normal for several weeks.

*Clinical Implications.* Much recently has been written concerning the effects of a low serum and a low cellular potassium concentration and alert clinicians now are aware of the clinical manifestations of hypokalemia.[7]

The plethora of articles extolling the virtues of potassium therapy has, however, left many clinicians a little confused as to the metabolic rationale of such therapy. In the immediate postoperative period potassium diuresis is a dominant characteristic of the response of the body to trauma, and parenterally adminis-

tered potassium is excreted in the urine along with endogenous potassium. The negative potassium balance which occurs during these few days despite potassium administration is usually of little or no clinical importance if not unduly prolonged. Potassium is excreted by the kidney and when administered to an oliguric patient—a common postoperarive condition—may result in signs of potassium toxicity. It seems evident, therefore, that it is both unnecessary and occasionally unwise to add potassium supplement to the intravenous fluids of the usual uncomplicated postoperative case.

By the time that intravenously administered potassium is utilized by the body and not merely excreted in the urine, the patient usually is taking fluids by mouth. The need for intravenous potassium has then passed. As is the case with protein administration, the anabolic phase of tissue regeneration begins at about the same time as food can be taken by mouth. Potassium or protein administered prior to that time is of little value.

Such a program of therapeutic nihilism should be followed only in the uncomplicated case. Where prolonged fasting, diarrhea, or loss from intestinal fistulas may occur, potassium losses obviously are abnormal and parenteral potassium administration is necessary. Such cases, fortunately, are relatively rare in the usual surgical practice.

### MISCELLANEOUS METABOLIC RESPONSE TO TRAUMA

1. *Temperature and sweating.* Following serious trauma, there is a slight rise in body temperature which occurs independent of bacterial infection. This temperature elevation of ¾ to 1 c. has been shown to be correlated with decreased sweating. The implication is that such a slight hyperthermia may be due to a decreased ability to lose heat.[10] Obviously this minor temperature change should not be confused with postoperative pyrexia of more common etiology.

2. *Gastrointestinal secretions.* Following trauma there appears to be a marked diminution in the volume of the succus entericus[9] which returns to normal about the fourth day. Following abdominal surgery, this may diminish distention in the patient whose intestines are immobilized by postoperative ileus.

3. *Thyroid activity.* Following stress there is a transient though very minor increase in thyroid activity, as measured by protein bound iodine and $I^{131}$ measurement. The evidence in this regard is controversial.[31]

4. *Renal function changes.* Although there are marked changes in renal function during anesthesia, kidney function returns to normal within a very short period.[20] The cause of abnormal urinary output and electrolyte balance in the postoperative period in the usual case must be sought outside of the kidney.

5. *Carbohydrate metabolism.* Following trauma, characteristically there is an insulin-resistant hyperglycemia and glycosuria which has been called postsurgical diabetes.[12] This carbohydrate dysfunction apparently is due to a decreased utilization of carbohydrate and an increased formation of glucose secondary to protein catabolism. These abnormalities result in an abnormal glucose tolerance test in the early postoperative period[23] and may result in inefficient utilization of intravenously administered glucose solutions.

6. *Clotting factors.* Immediately following trauma there is a slight fall in the circulating prothrombin and platelet level, which reaches a maximum on the second to fourth day. By the tenth day the platelets are normal. These changes, which are of such importance in the postoperative and post-traumatic period, are not thoroughly understood.[30]

7. *Fibroblastic activity.* Following operation there is normally a 3 to 4 day lag period in the process of tissue repair. Thereafter, during the fourth to seventh postoperative days, a tremendous fibroplastic and connective tissue reaction occurs, bridging the gap in the tissues and adding strength to the wound. We now know that this early delay in the initiation of fibroplasia is caused by the excess circulating adrenal corticoids[13] and when these compounds of the E and F type are withdrawn, fibroplasia proceeds.[8]

## SUMMARY

In summary, we have reviewed the course of the metabolic response of the body to trauma. Many of these chemical and metabolic changes can be ascribed to the known actions of adrenal cortical hormones which are prominently increased following stress. The clinical significance of the response to trauma has been indicated in the discussion of each major alteration. Emphasis has been placed on practical methods of meeting these metabolic changes so that the clinician can provide the patient with the correct fluids and electrolytes in the period following stress or operation.

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# THE SURGICAL TREATMENT OF PERFORATED PEPTIC ULCER

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We wish to report our experience with 100 consecutive unselected cases of gastroduodenal perforation due to benign peptic ulceration. They occurred in Denver, Colorado over the seven year period from July 1946 to July 1953. Each case was treated by one or the other author or by the authors jointly. The majority were indigent patients cared for at the Denver General Hospital on the Surgical Service of the University of Colorado School of Medicine. The remainder were from the private practice of the authors. Many of these people came from low strata of society and suffered from malnutrition, alcoholism or other chronic disease. Eighty-nine of the perforations were duodenal, 10 were gastric and 1 was jejunal.

Of the 100 patients with gastroduodenal perforations, 8 died without operation, their disease being discovered at autopsy. In this group, 2 perforated while in the hospital; 1 was in because of carcinoma of the prostate with extensive metastasis and the other had severe cardiac decompensation. The remaining 6 came into the hospital moribund and died shortly after admission, also with their disease unrecognized. Of these, the youngest was 71 and the oldest 79 years of age. Ninety-two were operated upon. In this group there were also 8 deaths, with an operative mortality of 8.7 per cent. The over-all mortality rate was 16 per cent.

The age of the patients is depicted graphically in figure 1. The youngest was 21 and the oldest 89 years of age. There was a slightly higher percentage of older patients in our series than in that reported by De Bakey[2] in his collective review of 6,875 cases. About half of our patients were between 40 and 60 years of age. We found no reason for this except perhaps that the younger patients have less tendency to migrate to a charity hospital than do the older group. Whatever the explanation, the fact is that the incidence of perforation in our series rises sharply after the fortieth year and decreases almost as abruptly after the sixtieth year.

Ninety-five of the patients were men and 5 were women. A break-down of the racial background indicates that race is probably not an important factor in the incidence of this disease in this particular locale. Ninety patients were either white or Spanish-American, 8 were Negro, 1 was Indian and 1 Japanese. Here, race apparently offers no immunity to this disease.

A concerted effort was made to establish in each case the duration of the ulcer history preceding the perforation. Nine per cent of the patients operated upon steadfastly denied having had ulcer symptoms longer than a day or two before the perforation. A number of patients gave this history on admission, but later admitted symptoms of longer duration. Nineteen per cent claimed to have had symptoms for less than one year, but by far the majority (72 per cent) had had

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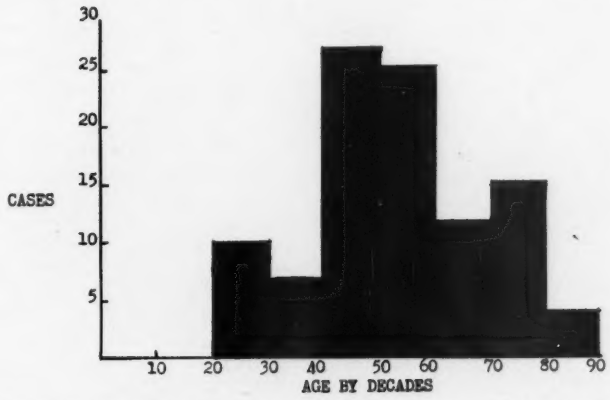


FIG. 1. Seventeen per cent of the patients in this series were under 40 years of age, 52 per cent were between 40 and 60, and 31 per cent were over 60.

symptoms for a considerably longer period. Five of the patients had had previous perforations.

It is our opinion that alcoholism is an important predisposing factor in this remarkable disease. Forty per cent of the patients frankly admitted an alcoholic history of some proportion and it is our belief that, if the truth could be obtained, an even greater number would fall in or near the category of confirmed alcoholism. This may be attested to by the fact that of the 9 postoperative patients who developed delirium tremens, 3 denied previous alcoholic intake.

In our group, sudden abdominal pain, often at the time of some moderate physical activity such as twisting, turning or stooping, usually heralded the onset of the perforation. The pain was upper abdominal first and frequently spread to the right side of the abdomen. As a rule the onset of pain was sudden. In the perforations which leaked only a small quantity, however, the pain was likely to occur more gradually and less likely to reach the intensity seen in patients with extensive peritoneal contamination. More than a third of the patients had pain referred to one or both shoulders.

Marked involuntary rigidity of the anterior abdominal musculature usually was present and was described as *board-like* 70 per cent of the time by the initial examiner. Thirty per cent of the patients had something less than board-like rigidity when initially examined and 7 per cent had little or no rigidity. It was our experience that lack of involuntary abdominal wall rigidity occurred when the patient was too aged and ill from another disease or from far advanced peritonitis to muster this defense mechanism. Contrary to the generally accepted description of this disease, 47 per cent of our patients vomited after the onset of the perforation. In 10 per cent the vomitus contained blood, although none had a massive hemorrhage.

Frequently these patients were described by the intern as being in shock, but pulse and blood pressure recordings did not confirm this impression in the early

TABLE I

| Hours from perforation to roentgenologic examination | Per cent of patients with demonstrable free intraperitoneal air |
|---|---|
| 0–6 | 57% |
| 6–12 | 68% |
| over 12 | 77% |

TABLE II

| Type of Closure | Cases (Total 92) |
|---|---|
| Graham | 85 |
| Primary resection | 2 |
| Plication | 2 |
| Pezzar catheter | 1 |
| Purse string | 1 |
| No repair (spontaneously sealed) | 1 |

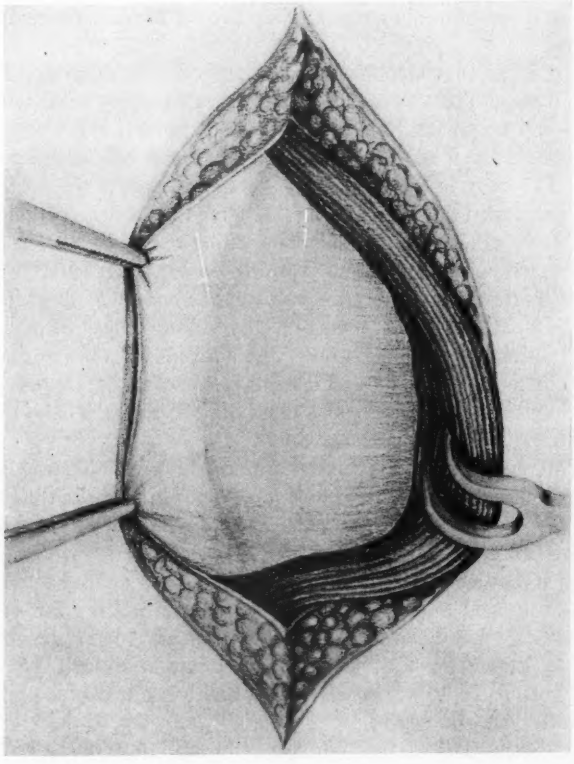

FIG. 2. The rectus muscle is dissected away from the midline and retracted to the right, carefully preserving its blood and nerve supply.

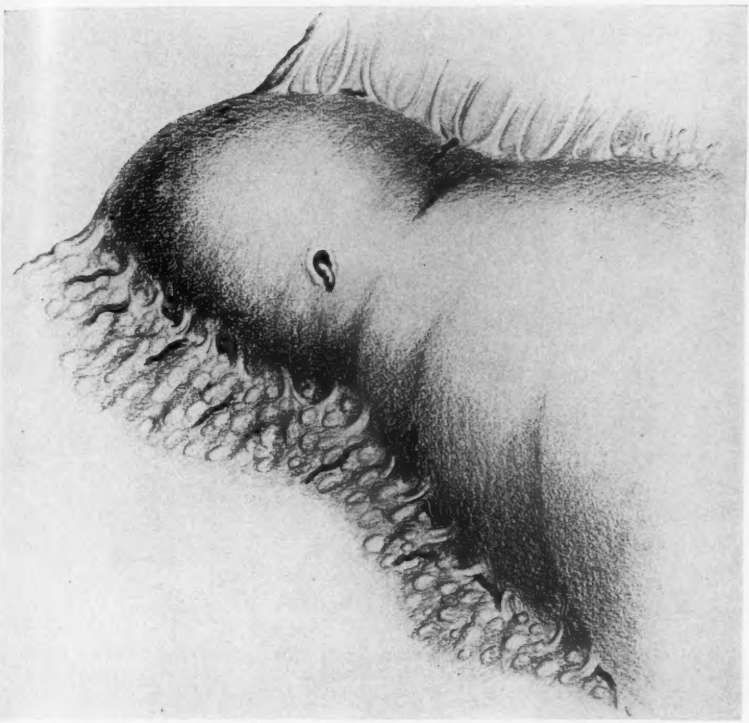

FIG. 3. This is the approximate position of 90 per cent of the perforations in this series.

perforated ulcer. As was pointed by Wangensteen,[7] and as was true in this series, shock is a late manifestation of this disease indicating advanced generalized peritonitis. In fact, true shock within six hours of the onset of symptoms should make the surgeon suspicious that perforated peptic ulcer is not the cause of the patient's pain.

Free intraperitoneal air demonstrated by roentgenogram is a finding of considerable importance in helping to establish the diagnosis. All the patients operated upon in this study were subjected to abdominal roentgenographic examination preoperatively and free air was demonstrated in 68 per cent. This figure is somewhat higher than has been reported in other series[5] and is worthy of comment. We believe that the lateral decubitus film with the right side up is more valuable than is the upright film. When the diaphragm is poorly delineated and the quantity of air in the peritoneal cavity is small, it may be difficult to differentiate between air in the abdomen and air in the lung in the upright film. A small quantity of air is more easily visualized in the lateral decubitus position between the relatively dense liver and lateral chest wall. It is also true that the longer the perforation exists before the roentgenogram the greater is the likeli-

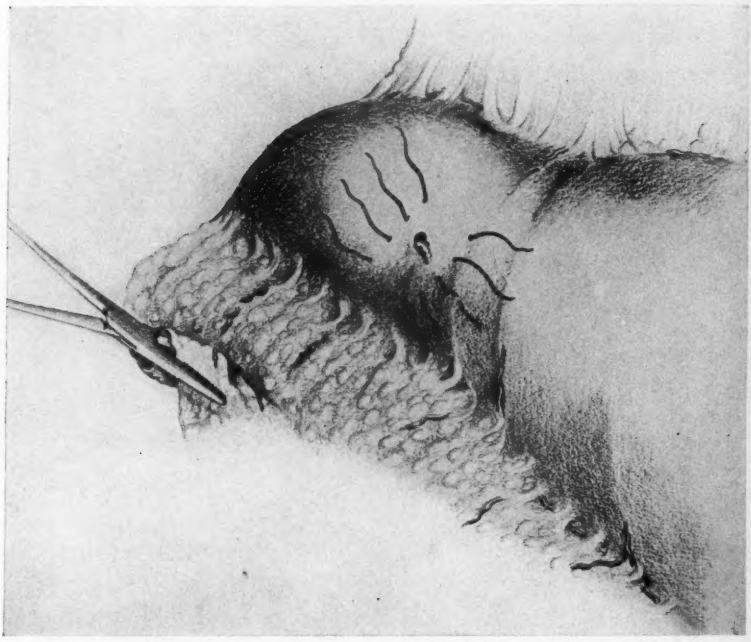

FIG. 4. Sutures should be placed far enough away from the perforation that they do not tear through the edematous duodenal wall. A free omental graft is to be taken distal to the point indicated by the hemostat.

hood of demonstrating free air in the peritoneal cavity. The following figures illustrate this point (table I).

Early in the series we used several methods of closure of the perforation in an effort to find one that seemed satisfactory. Table II enumerates the methods used.

The Graham[4] type closure proved to be an easy and safe method of accomplishing the end and this method was adopted for the majority of cases. The accompanying drawings (figs. 2 to 5) depict the use of the free omental graft and is the method used exclusively by one of us (HTR). Even though it is somewhat more time consuming, we prefer to retract the rectus muscle as it helps preserve its nerve and blood supply. This is especially important in a wound such as this that may be contaminated with duodenal contents, since dehiscence is a major postoperative complication.

Table III indicates the approximate size of the perforations seen in this series.

Most of the perforations 10 mm. in diameter or over occurred in patients who had been perforated more than 12 hours before they were admitted to the hospital. However, it did not necessarily follow that all perforations over 12 hours old were large.

The time that elapsed between the perforation and its closure materially influenced the mortality rate. Thirty-eight per cent of our patients were operated

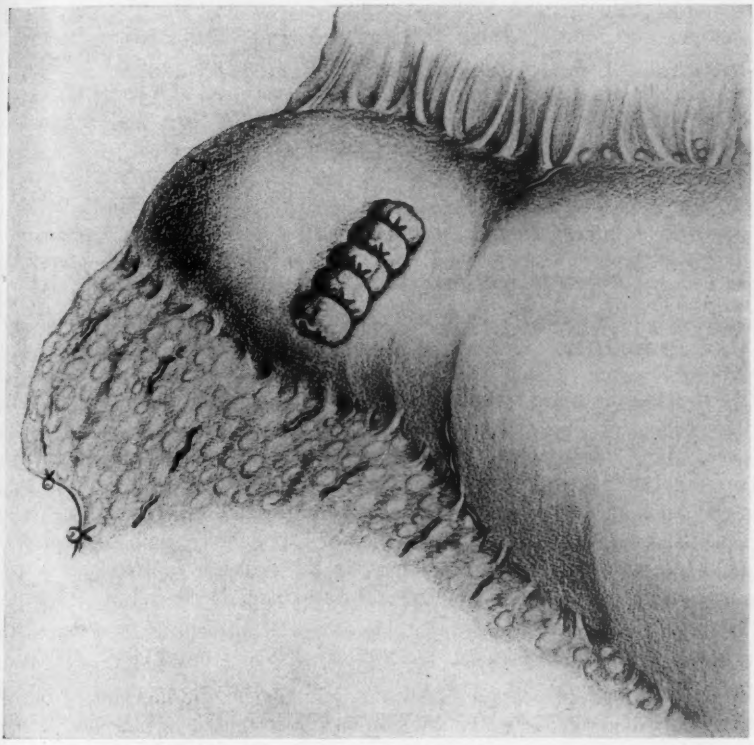

FIG. 5. The free omental graft is tied in place, sealing the perforation.

upon in the first six hours. In this group there were no deaths. Likewise, 38 per cent of the patients were operated upon between the sixth and twelfth hours, but in this group the mortality rate was 11.4 per cent. In the remaining 24 per cent, who perforated more than 12 hours before operation, the mortality rate was 18.1 per cent (Table IV).

In addition to the 8 patients who died without operation, there were as previously stated, 8 patients who died postoperatively. Of this group 4 were shown by autopsy to have died of peritonitis. One died of a pulmonary embolus on the seventh postoperative day, 1 had a cerebral vascular accident on the table, but survived five days, and 1 died on the nineteenth day of bronchopneumonia. One man, age 51, had cardiac arrest on the operating table. He had an emergency thoracotomy and cardiac massage. Cardiac rhythm was re-established but he died 48 hours later.

There were no deaths in the patients under 50 years of age. Two patients who died were in their fifties, 3 were in their sixties and the remainder were 70 or older. For unknown reasons, the older patients arrived at the hospital later for treatment. We believe that the combination of advanced age and the longer time

TABLE III

| Size of Perforation | Per cent of Total Perforations |
|---|---|
| 0–5 mm. | 70 |
| 5–10 mm. | 17 |
| over 10 mm. | 13 |

TABLE IV

| Hours from perforation to operation | 0–6 | 6–12 | over 12 |
|---|---|---|---|
| Per cent of total patients (92) operated upon | 38% | 38% | 24% |
| Deaths (total 8) | 0 | 4 | 4 |
| Mortality in per cent | 0 | 11.4% | 18.1% |

between perforation and treatment undoubtedly explains the higher death rate in this group.

There were 12 postoperative wound dehiscences of some degree, most having occurred in the first year of our study. Three of these patients died, but in only 1 was the dehiscence considered to be a contributing factor. Three patients had clinical thrombophlebitis, 1 of whom died of a pulmonary embolus. Intraperitoneal abscess developed postoperatively in 3 instances. One responded to intensive antibiotic therapy and the other 2 were drained surgically.

## COMMENT

During the past 10 years a significant reduction in the mortality from this disease has occurred. The antibiotic and chemotherapeutic agents have unquestionably been the most important single factor in this gratifying trend. The use of whole blood and a better understanding of fluid, ionic, caloric and vitamin requirements have added greatly to effective treatment. Gastric suction in preparation for operation and for 48 to 72 hours after operation has been a vital step. In spite of these facts, the commonest cause of death is still peritonitis.

We have had no significant experience with the nonoperative method of treatment of perforated peptic ulcer. One patient had sealed spontaneously at the time of operation and there were several others in whom it was apparent that sealing was in progress. However, after seeing 13 per cent of this group with large perforations that most likely would never seal, and having successfully closed perforations that had been present for 120 hours, it is our conviction that we have absolutely no way of knowing which perforation should be treated by the conservative method. In the patient operated upon we have the assurance that a proper diagnosis has been made, and that the perforation has been sealed by a tried method rather than by the perchance adhesion to some adjacent structure.

It has been stated that perforations more than 24[6] hours old should not be operated upon since, in the face of advancing bacterial peritonitis, any operative procedure would be poorly tolerated. Admittedly our experience is small, but

we believe that this concept is perhaps too arbitrary. As mentioned, we have seen a number of perforations beyond the 24 hour mark in which no spontaneous attempt at sealing had taken place. In these instances, a potentially lethal internal duodenal fistula was present. Had not surgical closure been done we believe that these patients would not have survived. It goes without saying that, particularly in these older perforations, time should be taken to restore fluid and electrolyte balance before surgery.

Only 2 of our patients were treated by primary partial gastric resection. Both were seen within the hour of perforation; had minimal peritoneal contamination; gave a long ulcer history and were in good physical condition. Both survived; had uncomplicated postoperative courses and have remained symptom free. We, of course, recognize the trend toward broadening the indications for primary partial gastric resection[1, 3] and we appreciate the advantages of dealing definitively with the ulcer at the time of perforation. Because patients who have massive peritoneal contamination often are extremely sick after even simple suture, we have been hesitant to add the possibility of the failure of the duodenal stump to heal or a malfunctioning gastrojejunostomy to the woes of this group. We are at the present time studying the problem of whether or not the rigid criteria used in our two primary partial gastric resections should be relaxed.

It is worth repeating that large perforations are associated with a poor prognosis. Of our 8 postoperative deaths, 5 (60 per cent) had perforations larger than 10 mm. in diameter. All the large perforations occurred in older debilitated patients, and although they were treated by suture of the perforation which seemed the simplest form of treatment, a glance at the mortality rate would indicate that almost any other form of treatment would be an improvement. It is probably the truth that this small percentage of the total number of patients with perforated ulcers are poor risks for any form of treatment.

Follow-up studies have been largely unsatisfactory in our group because of the many transients. We believe, however, that the occurrence of a perforation and its surgical closure does nothing to alter in any way a patient's ulcer diathesis. Postoperatively, many are relieved of their symptoms wholly or in part for varying lengths of time. This may be due to the fact that in the postoperative period many of the patients receive for the first time proper medical management of their ulcer. We believe that most patients who suffer a perforation have an intractable problem and that sooner or later they will have recurrence of symptoms. We consider the surgical closure of a perforated peptic ulcer a stop-gap in the definitive treatment of this disease, the definitive treatment at the present time being either primary or secondary partial gastric resection.

## SUMMARY

We have reviewed 100 consecutive, unselected cases of gastroduodenal perforation due to benign peptic ulceration that have occurred in the experience of the authors over the past seven years. Ninety-two were operated upon with an operative mortality rate of 8.7 per cent. Eight died with the diagnosis unrecognized or before operation could be tolerated. Half of the patients were between

40 and 60 years of age and 95 per cent were men. Seventy-two per cent gave a long history of ulcer and 70 per cent presented with the physical finding of a board-like abdomen.

Free intraperitoneal air was demonstrated radiographically in 68 per cent. Eighty-five per cent had a Graham closure. There was no mortality in the group of patients operated upon within six hours of their perforation nor in those less than 50 years old. The commonest cause of death in our series was peritonitis. Of the eight postoperative deaths 5 of the patients had perforations that were larger than 1 centimeter in diameter.

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# THE CYSTIC DUCT SYNDROME

## REPORT OF THREE CASES

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Patients with postcholecystectomy complaints are common. Patients with postcholecystectomy complaints in whom a specific remedial etiology can be found are uncommon. Among the latter are those patients in whom a dilated cystic duct stump can be shown to be the cause of the persistent symptoms. Excision of the dilated duct stump will give complete relief of their symptoms in a high per cent of cases.[7]

There are surprisingly few articles devoted to this subject in the literature. Beye[1] in 1936 was one of the first to emphasize the importance of the *reformed gallbladder*. Womack and Crider[7] reported 5 cases in 1947. Other authors who have reported such cases include Gray and Sharpe,[3] Hicken, White and Coray,[4] Peterson,[6] Morton,[5] and Garlock and Hurwitt.[2] All agree that a dilated cystic duct, with or without calculi, can cause a persistence of much the same symptomatology the patient experienced prior to the cholecystectomy. Three additional cases are here recorded.

### CASE REPORTS

Case 1: Denver General Hospital. L. M. a 36 year old white housewife was admitted July 14, 1953 with a chief complaint of severe right subscapular and right upper quadrant abdominal pain of 14 hours duration. The pain began as a sharp right upper quadrant pain which awoke her from her sleep. The pain radiated through to the right subscapular region and was accentuated about every five minutes with a knife-like exacerbation. It was accompanied by nausea and two episodes of vomiting.

Six years prior to her admission to the hospital she had had a cholecystectomy without common duct exploration at another hospital following a year of recurrent episodes of right upper quadrant abdominal pain without jaundice. She then remained free of symptoms, except for vague fatty food intolerance, until one year prior to admission when she was hospitalized for right upper quadrant abdominal pain at another hospital. She was discharged following a period of observation, which included a negative gastrointestinal roentgenographic series and a negative barium enema without a specific diagnosis. Six months prior to admission she had been hospitalized at the Denver General Hospital for three days observation for abdominal pain without a specific disease being found. Two weeks before admission she had an attack similar to her present episode for which she had spent two days in bed.

*Physical examination:* The temperature was 37.4 C., pulse 90, respirations 20 and blood pressure 180/120. She was a well developed obese white woman in no distress. Her skin was normal. The chief positive findings consisted of tenderness to deep palpation in the right upper quadrant of the abdomen. Murphy's sign was negative. There were no masses, muscle spasm or rebound tenderness. The remaining physical examination was noncontributory.

*Laboratory data:* The hemoglobin was 11.5 Gm. per cent. The hematocrit, white cell

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count, blood smear, urinalysis, serum bilirubin, albumin, globulin, alkaline phosphatase, thymol turbidity and cephalin flocculation, feces, and plasma prothrombin concentration were all within normal limits.

*Hospital course:* Plain roentgenograms of the abdomen, a gastrointestinal series, a barium enema, sigmoidoscopy and intravenous pyelograms were all within normal limits. On July 29, 1953 the biliary tract was explored. The duodenum, stomach, pancreas and liver were normal. The common duct was identified and found to be normal in size. It was opened and thorough exploration revealed no stones. Further dissection then exposed the cystic duct stump. This was enlarged (2 by 2 cm.) and thickened. When it was excised it was found to contain a facetted yellowish-green calculus 4 mm. in diameter (fig. 1). The lumen of the stump was 9 by 10 mm. in diameter. The stump was excised. The patient's postoperative course was uneventful. A cholangiogram made on Aug. 5, 1953 was normal.

*Follow up:* The patient was last seen six weeks following her operation at which time she was asymptomatic.


FIG. 1. The cystic duct stump excised in patient in case 1. Notice the facetted calculus and the blunted but nevertheless present valves of Heister.

Case 2: Veterans Administration Hospital, Fort Logan. J. W. a 53 year old man was admitted on Aug. 10, 1948, complaining of recurrent epigastric and substernal pain and indigestion for five months. In March 1948 he suddenly developed severe upper abdominal pain radiating to the precordium and the left shoulder region. This was accompanied by severe dyspnea. He was treated by his private physician for a coronary occlusion. From March until July in the same year he had frequent similar attacks and was hospitalized elsewhere on three occasions. All attacks were of similar nature; the pain was sharp and colicky, appearing first in the epigastrium, and radiated to the precordium and left shoulder and down the left arm. The pain always appeared two to three hours following eating and was accompanied by belching and slight dyspnea. He gained partial relief after the administration of nitroglycerine. While in the hospital and on a bland diet, the symptoms would quickly subside and he would be discharged, only to return in four to six weeks with a similar acute onset of pain. These attacks were never accompanied by a rise in temperature, vomiting, melena, jaundice or abnormal stools or urine. There was no association with effort or exercise. Many studies were made during the hospitalizations. Gastrointestinal series were said to have shown no abnormality of the stomach other than a 15 per cent 6 hour retention. A nonobstructed diverticulum 3 cm. in diameter in the second portion of the duodenum was demonstrated on several occasions. A barium enema showed multiple diverticula of the

large bowel. Cholecystography failed to reveal the presence of a gallbladder. On all occasions, the patient was seen by cardiologists and serial electrocardiograms were taken, but no definite diagnosis of organic cardiac disease could be made. One week prior to admission to the Fort Logan Veterans Administration Hospital the patient had another similar attack, and for the first time mild jaundice, dark urine, and light colored stools were noted. Since the onset of the present illness, there had been no appreciable weight loss.

*Past history:* There was a past history of possible malaria as a child. An appendectomy following an acute episode of right lower quadrant pain, was done in 1922. From 1937 to 1939, he had several attacks of epigastric and lower substernal pain with jaundice, and a cholecystectomy was done in 1939. He was free of symptoms except for intolerance of fatty foods from that time until 1947. Fatty foods tended to bring on belching and a heavy feeling in the stomach.

*Physical examination:* (August 1948) He was a well developed obese man in no acute distress. The blood pressure was 98/64 and heart sounds were regular. There were right upper quadrant and right lower quadrant abdominal scars. There was slight tenderness in the epigastrium to the right of the midline. No masses were palpable, and peristaltic sounds were normal. There was no jaundice.

*Laboratory data:* The red cell count, hemoglobin, white cell count, bleeding time, clotting time, plasma prothrombin concentration, icterus index, serum cholesterol, blood carbon dioxide combining power, and urinalysis were all within normal limits.

*Roentgenograms:* Chest essentially negative. Films previously made referrable to the gastrointestinal tract were reviewed; they showed nothing pertinent. An electrocardiogram was within normal limits.

*Hospital course:* The patient remained free of pain. At operation on Aug. 20, 1948 dense adhesions were found in the right upper quadrant of the abdomen. The common duct was considerably dilated, but no stones were palpable. It was opened and probed. No obstruction was found distally, but in the right hepatic duct near its junction with the left hepatic duct there was definite obstruction. This proved to be due to extrinsic pressure caused by a dilated cystic duct stump. Following excision of the stump (fig. 2) the right hepatic duct then admitted a probe easily. A T tube was placed in the common duct. The postoperative course was uneventful and the patient was discharged Sept. 10, 1948.

*Follow up:* The patient was last seen on Oct. 21, 1953 at which time he stated that he had been completely free of jaundice, fatty food intolerance, and abdominal pain since excision of the cystic duct stump. He had however continued to have pain almost daily in the left anterior chest and shoulder region. This pain was undoubtedly related to an old severe fracture and soft tissue injury to the upper left arm.

Case 3: Veterans Administration Hospital, Albuquerque, N. M. J. S. a 40 year old Spanish-American man was admitted June 12, 1953 complaining of abdominal pain of two weeks duration. He stated that two years prior to admission he had had a cholecystectomy and exploration of his common duct. A tube was left in the middle of the wound which drained bile. This tube was removed one month postoperatively. Following removal of the tube, he had some pain in the site of the previous wound. This pain remained and had bothered him since. However, in the last two weeks prior to admission he had developed severe pain at this site. He stated he had pain standing and when lying on either side. However, the pain was much decreased when lying on his back. He also stated that in the last two weeks he had had some pain radiating through to the back, which was the same type of pain he had prior to his cholecystectomy. There was no recent history of jaundice, discoloration of urine, or light colored feces. There had been no vomiting, but his appetite had been poor in the last two weeks.

*Physical examination:* The patient was a short obese man in moderate distress from right upper quadrant pain. The pulse was 88 and the blood pressure was 140/90. The chief positive physical findings consisted of a tender palpable hernia in the midportion of the cholecystectomy scar, and a moderately enlarged liver.

*Laboratory data:* The white cell count was 10,250 per cu. mm. and the serum thymol

turbidity was 6.8 MacLagan units. The urinalysis, blood smear, red cell count, hemoglobin, bleeding time, clotting time, serum albumin, globulin, bilirubin and cephalin flocculation were all within normal limits.

*Hospital course:* Roentgenographic films of the chest and abdomen showed nothing contributory. A gallbladder series on June 19, 1953 failed to reveal a definitely outlined gallbladder shadow. There was no evidence of opaque calculi. Several ill-defined densities were seen which were believed to represent fecal material in the bowel. A gastrointestinal series was normal. Further laboratory studies included serum amylase, fasting blood sugar, bleeding time, clotting time, serum protein, serum albumin, and cephalin flocculation test all of which were within normal range.


FIG. 2. The cystic duct stump excised in patient in case 2. This was incorrectly labelled recurrent gallbladder.

An exploratory laparotomy was done on July 10, 1953. The common duct was found to be normal in size and to contain no calculi. Further dissection revealed a much enlarged and thickened cystic duct stump which measured approximately 3.5 cm. in length. It contained no calculi. This was excised and the patient's postoperative course was uneventful. The common duct drainage tube was removed on July 23 following a normal cholangiogram and the patient was discharged asymptomatic on Aug. 17, 1953.

*Follow up:* The patient was last seen about two and one-half months following his operation at which time he stated that he had had none of his preoperative symptoms.

## DISCUSSION

These three patients are excellent examples of the cystic duct syndrome as described by others. The first patient (case 1) is of unusual interest because of the colicky component of her pain and the calculus within the dilated cystic duct. It is important to point out that the calculus found at operation was larger than the lumen of the cystic duct at its entrance into the common duct. It is also important to note that this was a calculus with several facets, and that there were no calculi in the common duct. Thus in this patient the calculus undoubtedly was trapped in the cystic duct at the time of the cholecystectomy and that originally it was one of many within the gallbladder. It remained relatively quiescent, except for mild fatty food intolerance, for five years. At the end of this time she began having her recurrent attacks of colicky pain with vomiting. The long interval between her cholecystectomy and the recurrence of her precholecystec-

tomy symptoms is of considerable interest. It demonstrates clearly the fact that some of the patients with the cystic duct syndrome may experience a relatively long period of relief from their preoperative symptoms before the postoperative return of the symptoms. This fact alone should make one suspicious of the possibility of the cystic duct syndrome.

The patient in the second case was even more of a diagnostic problem because of the substernal pain which radiated down his left arm coincident with his epigastric discomfort. This type of pain, until his jaundice appeared, made angina pectoris a troublesome possibility.

The unusual length of the cystic duct remaining in the patient in the third case calls attention to what is probably the major reason why this syndrome exists. It seems apparent that, because of the ever present danger of common duct injury and its unhappy sequelae, that some surgeons stay as close to the gallbladder as possible when dividing the cystic duct. It would seem much more logical to obtain an accurate and clear dissection of the cystic duct and its entrance into the common duct. This would ensure a division of the cystic duct close to the common duct and thus avoid the blind pocket of the cystic duct stump or the possibility of trapping small calculi within the cystic duct.


## SUMMARY

Three additional cases of the cystic duct syndrome are reported.

The cystic duct stump which remains following cholecystectomy can give rise to symptoms which are often similar to the patient's preoperative symptoms.

It is suggested that careful attention be directed to the length of cystic duct remaining during cholecystectomy.


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# INTRALUMINAL PRESSURES IN THE INTERNAL CAROTID ARTERY OF NORMAL HUMAN BEINGS

## EFFECTS OF OCCLUSION OF ASSOCIATED ARTERIES

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Interruption of the carotid stream with the resultant diminution in blood volume circulating to the homolateral side of the brain produces serious neurologic sequelae or death in a significant proportion of cases. In general, sacrifice of all or part of the carotid tree is done as a deliberate step only in the treatment of malignant tumors of the neck or in the treatment of intracranial aneurysms. The risk of ligation for cervical neoplasm is considerably greater than the risk for intracranial aneurysm. Thus, for neoplasm, Vosseler and Ficara[13] reported a mortality rate of 19 per cent, Pemberton and Livermore[10] 30 per cent, Lahey and Warren[6] 37.5 per cent, Martin and associates[8] 40–50 per cent, Watson and Silverstone[14] 55 per cent and MacComb[7] 58 per cent. On the other hand for intracranial aneurysm, Bassett and Gass[1] report the much lower mortality figure of 4.5 per cent, Rogers[11] 4.5 per cent, Dandy[3] 4 per cent, and Sweet, Sarnoff and Bakay[12] 5.1 per cent.

The belief is still widely held that ligation of the common carotid, leaving the external carotid intact is less dangerous than ligation of the internal carotid because of the possibility of retrograde flow via the external carotid. For example, Dorrance[4] has stated: "The retrograde flow from the anastomoses of the external carotid down the external, past the bifurcation, and into the internal has been recognized by at least 20 authors whose writings have been brought to our attention." Similarly, Keegan[5] states, "Ligation of the common carotid artery usually permits a continued circulation through the internal carotid, by the abundant anastomoses of the external carotid artery and reversed current through it into the internal carotid artery." Rogers has indicated his support of this concept as follows: "In a reasonably fit person I have no hesitation in stating that division of the common carotid artery is a safer operation. This statement does not apply to the internal carotid artery." Based on the accuracy of this hypothesis, Conley[2] has even suggested anastomosis between the internal and external arteries after bulb excision as a means of reducing the hazards.

It is our belief that this concept is erroneous and that it is just as dangerous to ligate the common carotid as it is to ligate the internal carotid artery and that the patency of the external carotid artery does not alter the picture in any way whatsoever. The first objective evidence in support of our belief came from Sweet, Sarnoff and Bakay[12] who made intraluminal pressure studies on the internal carotid artery in 22 patients. They demonstrated convincingly that

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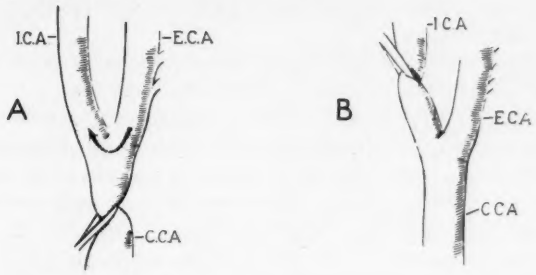
## INTRA-LUMINAL PRESSURE IN INTERNAL CAROTID ARTERY OF NORMAL HUMANS




### THE PROBLEM

WHEN THE COMMON CAROTID IS OCCLUDED (A) IS THERE AN EFFECTIVE RETROGRADE FLOW INTO THE INTERNAL CAROTID ARTERY FROM THE EXTERNAL CAROTID ARTERY THAT MAKES INTERRUPTION OF THE COMMON CAROTID A LESS HAZARDOUS PROCEDURE THAN INTERRUPTION OF THE INTERNAL CAROTID ARTERY (B).

FIG. 1

opening and closing the external carotid artery did not favorably alter the intraluminal pressure in the homolateral internal carotid artery except in the rarest of cases. Their work was open to some theoretical objection due to the fact that it was done on patients with intracranial aneurysms or suspected brain tumors. The question naturally arose whether the results obtained in these patients with known cerebral circulatory abnormalities would apply to patients with presumably normal circulations.

*Methods of Procedure:* Our study was made on 12 patients who were operated upon for illnesses in no way related to cerebral disturbances and who were therefore presumed to have normal circulatory patterns. Our purpose was to obtain objective evidence of the effect or lack of effect of associated external carotid artery occlusion on the intraluminal pressures of the internal carotid artery by occlusion of the common carotid (fig. 1). The age of the patients ranged from 32 to 70 years. No difference in response was noted because of age, but our series is too small to draw any conclusions on this factor. The diagnoses ranged from those patients having a simple thyroidectomy to patients receiving such operations as radical neck dissections, and combined neck and jaw resections. In the latter type of operation no permanent interruption of the carotid tree was done, the cervical metastases being dissected free of the carotid arteries.

Following pentothal induction an endotracheal tube was inserted and the patient was then carried on nitrous oxide and ether. The experimental studies were not made until the operations had been largely concluded so that the patient

had been anesthetized for periods ranging from 45 minutes to 3 hours. Prior to the insertion of the needle into the lumen of the internal carotid artery, the carotid bulb itself was infiltrated with procaine with the objective of nullifying any reflexes stemming from stimulation of the carotid sinus that might interfere with the experiment.

A hypodermic needle was then placed into the lumen of the internal carotid artery and this needle was connected to a plastic tubing filled with 5 per cent dextrose solution. The tubing led away to a strain gauge apparatus that contained a *wheatstone bridge* electrical circuit. The hydrostatic pressure waves transmitted through the plastic tubing were converted into electrical impulses which were recorded by a galvanometer. The needle of the galvanometer had a tiny mirror attached to it on which a light was played constantly when the machine was in operation. Deviations in the galvanometer needle thus produced changes in the angle of this mirror and the reflected light rays were directed into a camera and produced tracings on photographic paper contained therein. Adequate gauges permitting recordings of elapsed time and pressure changes measured in terms of millimeters of mercury were included. A photographic record was thus obtained which permitted an accurate analysis of the intraluminal pressure changes in the internal carotid artery. Once the apparatus is set up and in position, a total elapsed time of two or three minutes suffices to obtain all of the necessary information.

*Results:* The results obtained on the internal carotid pressures by the above technic showed a gratifying uniformity. Moreover, this uniformity could be produced at will in the same patient regardless of whether the measurements were taken at the beginning, middle, or at the end of the operation and were not

TABLE 1

*Mean intraluminal pressure in internal carotid artery*

(Effect of Occlusion of Associated Arteries Recorded in mm. Hg in 12 Patients with Presumably Normal Cerebral Circulations)

| Case # | Diagnoses | Press. Int. Car. Prior to Occlusion | Press. Int. Car. with Com. Car. Occl. | Press. Int. Car. with Com. and Ext. Car. Occl. | Press. Int. with Ext. Car. again Patent |
|---|---|---|---|---|---|
| 1 | Nontoxic adenoma, thyroid | 82 | 49 (60%) | 50 | 50 |
| 2 | Carcinoma, parotid gland | 67 | 31 (47%) | 31 | 30 |
| 3 | Nontoxic adenoma, thyroid | 123 | 70 (57%) | 65 | 66 |
| 4 | Adv. basal cell Ca of eyelids | 93 | 55 (59%) | 54 | 53 |
| 5 | Carcinoma, thyroid | 98 | 57 (58%) | 60 | 59 |
| 6 | Carcinoma, gum | 97 | 77 (80%) | 77 | 77 |
| 7 | Carcinoma, larynx | 87 | 26 (30%) | 26 | 27 |
| 8 | Carcinoma, antrum | 106 | 66 (60%) | 68 | 68 |
| 9 | Carcinoma, pharyngeal wall | 102 | 58 (59%) | 60 | 61 |
| 10 | Carcinoma, tongue | 96 | 48 (50%) | 48 | 46 |
| 11 | Nontoxic adenoma thyroid | 88 | 44 (50%) | 46 | 46 |
| 12 | Carcinoma, tongue | 99 | 52 (52%) | 50 | 49 |

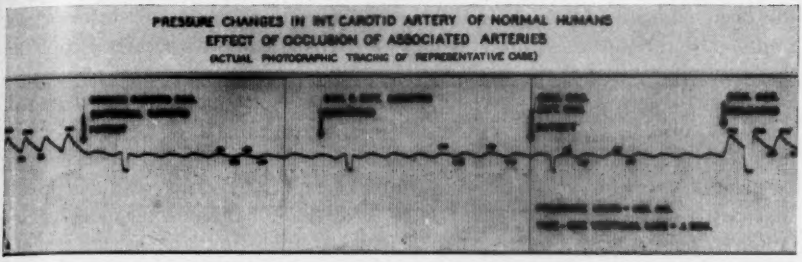



FIG. 2. The tracing starts with the needle in the lumen of the internal carotid artery with all arteries patent. The first arrow indicates the occlusion of the common carotid artery and the dip in the tracing is a signal indicating this occlusion. The remainder of the tracing is self explanatory. The results are typical in that a fall occurs within a few seconds after common carotid occlusion. When a stable level is reached, associated and repeated opening and closing of the external carotid artery has no effect. A return to preocclusion levels is reached within a few seconds after release of the common carotid.

affected by such factors as differences in age, sex, or changes in positioning of the head or body of the patient.

Within 6 to 12 seconds after occlusion of the common carotid artery there was a fall in the pressure in the internal carotid. As an average, this maneuver reduced the mean internal carotid pressures to approximately 55 per cent of the former levels. Case 6 was unusual in that a reduction to only 80 per cent (from 97 mm. Hg to 77 mm. Hg) was effected by common carotid occlusion. On the other hand, in one instance (case 7), a greater than average fall (from 87 mm. Hg to 26 mm. Hg) was obtained. With these 2 exceptions there was a great similarity in the degree of fall in the mean pressures of the internal carotid following occlusion of the common carotid (table 1).

When, in addition to occlusion of the common, the external carotid was also occluded no additional change was noted. In fact, when a stable level was reached following occlusion of the common carotid artery the associated and repeated opening and closing of the external carotid artery produced no discernible change in the photographic tracings. The pressure in the internal carotid artery remained at a consistently low level (averaging 55 per cent of preocclusion values) until the common carotid was released after which time the former levels were restored in a few seconds time (fig. 2).

## DISCUSSION

It will be seen that there is a definite similarity in the values obtained by Sweet and his co-workers on their patients with intracranial aneurysms or brain tumors and our patients with normal cerebral circulatory patterns. Yet, despite this similarity, the differences in the mortality rate when the carotid stream is interrupted in patients with intracranial aneurysms as compared with those in whom the carotid stream is interrupted for cervical neoplasms still exists.

Sweet thought that considerable help might be gained in selecting those patients in whom interruption of the carotid stream could be tolerated by noting

the degree of pressure drop in the internal carotid following occlusion of the common. In rare instances this may apply also to patients with cervical neoplasm. For example, in case 6, where the occlusion only reduced the distal pressure to 80 per cent of former levels, it would appear that occlusion may well be tolerated. Similarly, in case 7 where the occlusion produced a drop to 30 per cent of pre-occlusion values, it seems probable that serious complications would ensue from permanent interruption. With these 2 exceptions, however, no confident prediction in the remainder of the cases could be made. For these latter cases (which comprise the majority) we appear to be as far away as ever from selecting ahead of time those patients who will tolerate interruption and those in whom complications may be anticipated.

Martin[9] has reported on the experience on carotid ligations for cervical neoplasm at the Head and Neck Clinic of Memorial Hospital and his findings may be of some significance. A total of 88 consecutive cases of ligation were analyzed and there was no difference in the incidence of complications from common vs. internal occlusion. The cases studied covered the period from 1926 to 1952 and there was an over-all mortality rate of 31 per cent. However, a breakdown of the cases by years revealed that in the first 20 cases during the years 1926 to 1937 there was a mortality rate of 55 per cent, whereas in the last 34 cases covering the years 1948 to 1952 a mortality rate of only 12 per cent resulted.

A search was made for factors that may explain this reduction. The most significant disclosure appeared to be that "the greatest percentage of hemiplegia and eventual death occurs in those cases in which the ligation has been performed at a time when the blood pressure was low due to preceding hemorrhage or shock." A recommendation was then made that if ligation is necessary, it be deferred if possible until the blood pressure has been restored, the presumption being that the chances of deleterious complications are thereby lessened. He closes his discussion on the subject with the following note of caution: "Among the last 34 cases, with an over-all mortality rate of 12 per cent, as mentioned above, there occurred a series of 15 consecutive cases without a single death, while in the early nineteen-forties there occurred a series of 5 consecutive cases without a single recovery. The latter observations are mentioned here as a warning to those who may be inclined to interpret a high percentage of recoveries in a short series of cases as final proof of the effectiveness of some particular method of management."

The ill effects from carotid ligation may become manifest at once or may develop hours or even days later. A number of causes of delayed symptomatology have been suggested. In our opinion, the evidence is strongly in favor of the concept that ligation causes immediate diminution in blood flow to the brain. With the reduced blood flow, cerebral anoxia occurs, with resultant cellular damage and softening. The speed of the development of this lesion is related to the degree of circulatory insufficiency. Although in some cases postoperative thrombosis in the distal arterial segment may occur, as suggested by Dandy, this finding has been only occasionally confirmed in autopsy reports of other investigators. The use of postoperative anticoagulants, therefore, as advocated

by Pemberton and Livermore, while possibly increasing the factor of safety, should not be considered as eliminating the dangers inherent in ligation.

## SUMMARY AND CONCLUSIONS

Twelve patients with presumably normal cerebral circulations were studied with reference to intraluminal pressure in the internal carotid and the effect of occlusion of common and external carotid arteries on this pressure level.

There was an average fall in the mean pressure values distal to the site of occlusion to 55 per cent of preocclusion levels. Associated occlusion of the external carotid artery did not affect in any way the mean pressure level in the internal carotid when the common carotid artery was occluded. It is therefore just as dangerous to ligate the common as it is to ligate the internal carotid artery.

The difference in mortality rate when carotid stream occlusion is made for patients with intracranial aneurysm vs. patients with cervical neoplasm is contrasted. In occasional rare individuals, determination of the mean pressure in the internal carotid following occlusion of the common may be of some help in selecting candidates for permanent ligation, but in the majority of instances no confident selection can be made by this means.

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# EXPERIMENTAL AND CLINICAL OBSERVATIONS ON THE USE OF TANTALUM AND STAINLESS STEEL MESH IN HERNIA REPAIR

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*Denver*

## INTRODUCTION

The use of metallic prostheses as an adjunct to the repair of difficult hernias is not recent. Several metals were tried at the turn of the century, but quickly fell into disuse because they were either too rigid or biologically active with resultant sinus tract formation in the wounds. It was not until 1948 when Koontz[3] and Throckmorton[6] reported separately on the successful use of tantalum gauze mesh in hernia repair that interest was renewed. Since then other metals and plastic devices including stainless steel mesh[1, 5] have been tried.

Although the physical properties of stainless steel mesh are practically identical to those of tantalum mesh,[2] it would be of interest to compare the effects of their implantation in living tissue. A limited number of experimental and clinical observations are herein reported in an attempt to make such a comparison. The observations selected for assembling comparative data are those which appear to us most pertinent to the successful repair of hernias.

## MATERIALS AND METHODS

For purposes of experimental comparison of the two types of mesh, 16 mongrel dogs were used. They were anesthetized with nembutal sodium administered intravenously. Two defects were then created surgically on either side of the abdominal wall of each dog by removing segments of the rectus abdominis, internal and external oblique muscles down to the peritoneum. One defect (left side) was repaired with type 304 stainless steel mesh and the other (right side) with tantalum mesh.* Interrupted no. 000 cotton sutures were employed to anchor the mesh in place in 8 dogs. In the other 8 dogs, stainless steel monofilament wire was used to anchor the steel mesh, and braided tantalum wire was used to anchor the tantalum mesh. The wounds were routinely closed without drains with interrupted cutaneous sutures of no. 000 cotton. In 4 dogs, the wounds were purposely contaminated prior to closure by implanting 2 cc. of their own feces. Antibiotics in the postoperative period were not employed. All dogs were either killed or surgically explored under anesthesia two days to one year following implantations of the mesh.

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* Type 304 stainless steel mesh is marketed under the trade name Surgaloy Mesh and was furnished by Davis and Geck, Inc. The size of the mesh (50 by 50) and the size of the wire (3 mil.) in the mesh is exactly the same as in tantalum mesh. The latter was furnished by Ethicon Suture Laboratories.

The following comparative observations on the two mesh implants were recorded in each dog: (a) the degree of fibrosis around the mesh; (b) the degree of infiltration of the mesh by fibrous tissue; and (c) the presence or absence of fragmentation of the mesh. In 2 dogs (four implants) specimens for biopsies were taken of the fibrous tissue at the margins of the mesh.

The clinical material consists of 24 patients who had 29 hernia repairs in which one or the other type of wire mesh was employed. Interrupted no. 000 cotton sutures were used in all repairs for anchoring the mesh. Twenty-seven repairs were done for difficult postoperative ventral hernias, six of which were recurrent. One repair was for a large umbilical hernia and another for a recurrent left direct inguinal hernia. The period of follow-up observations has varied from 1 to 30 months, with an average period of follow-up observation of 12 months.

## RESULTS

The fibrosis in each of 12 dogs was grossly the same with both the stainless steel and tantalum sides (table I and figs. 1a and 1b).

Four of these dogs were those purposely infected and either died or were killed within the first week postoperatively. Their wounds were grossly infected and there was little fibrous reaction, the mesh lying essentially free with no apparent infiltration of the mesh with fibrous tissue. The other 8 dogs developed clean, well healed wounds.

TABLE I

*Observations on dogs with wire mesh implants*

Stainless steel was implanted in the left side of abdominal wall, tantalum in the right side

| No. of Dogs | Fibrosis encasing mesh denser on stainless steel side | Fibrosis infiltrating mesh denser on tantalum side | Fibrosis grossly same both sides |
|---|---|---|---|
| 16 | 4 | 4 | 12 |

FIG. 1(a)

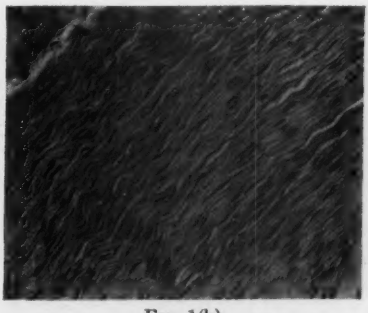

FIG. 1(b)

FIG. 1(a). Dog killed seven months following implantation of mesh. Stainless steel is in dog's left abdominal wall; tantalum is in the right. No gross differences in density of fibrosis.

FIG. 1(b). Same mesh as in figure 1(a) after its removal. Fibrosis infiltrating both types of mesh equally.

FIG. 2(a)

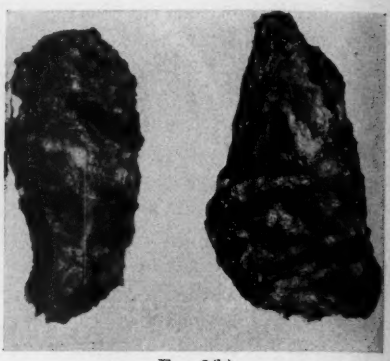

FIG. 2(b)

FIG. 2(a). Section from margin of tantalum.
FIG. 2(b). Section from margin of stainless steel. See text for description.

The 4 remaining dogs showed a denser fibrosis around the tantalum. The fibrosis infiltrating the tantalum mesh was, however, denser than that infiltrating the stainless steel. The wounds of these 4 dogs were clean and well healed. Sections of tissue were taken from the margins of either mesh in 2 dogs for microscopic comparison. In the sections obtained from the margins of the stainless steel mesh, there was more hyaline degeneration associated with more fibroblastic proliferation than in the sections from the margins of the tantalum mesh (fig. 2a and 2b). The significance of this observation made in only 2 dogs is questionable, but suggests (with the gross findings in the 4 dogs) that the stainless steel had provoked a greater fibrous tissue response than had the tantalum.

Fragmentation occurred in both meshes and to a comparable degree in 7 of the 16 dogs (fig. 3). In 9 dogs there was no fragmentation of either mesh. Fragmentation appeared to be related to the length of time the mesh had been present in the abdominal wall. This finding was present in the 6 dogs in which observations were made six months or longer following implantation. The other dog in which fragmentation was observed had the implants for only three months.

There were no grossly observable differences attributable to the different types of suture used for anchoring the mesh in place. Many of the cotton sutures, in contrast to the wire sutures, frayed out, presumably cut through by the wire mesh. However, the mesh remained in place.

In the group of patients in whom 29 hernias were repaired, tantalum was employed in 9 and stainless steel in 20 of the repairs (table II). There have been five known recurrences, four following repair with stainless steel and one following repair with tantalum. In three instances, twice where stainless steel and once where tantalum was employed, the recurrent hernias developed immediately adjacent to the margin of the mesh and are attributed to human error in that a larger sheet of mesh would probably have obviated the recurrence in each instance. The two remaining recurrences followed the use of stainless steel. One recurrence was through the center of the mesh which contained a fragmented

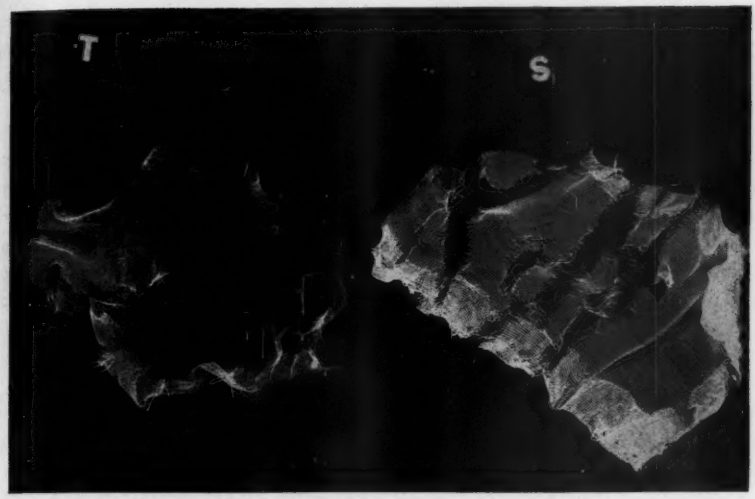


FIG. 3. Roentgenogram of both types of mesh removed from dog eight months following implantation. Fragmentation of both types.

TABLE II

| | No. of Patients | No. of Repairs | Recurrent Hernias | Fragmentation of mesh | Recurrences due to fragmentation | Postop. Complications |
|---|---|---|---|---|---|---|
| Stainless steel | 15 | 20 | 4 | 1 | 1 | 4 |
| Tantalum | 9 | 9 | 1 | 1 | 0 | 1 |

central defect as demonstrated roentgenographically. The other was not a true recurrence but is listed as such since a secondary plastic procedure was required. The original defect was so large that two sheets of stainless steel were employed with overlapping of the margins at the central portion of the defect. Convalescence was complicated by draining sinuses requiring removal of the mesh and skin grafting with an ultimate satisfactory result as observed nine months later.

Fragmentation of tantalum was observed in 1 case of recurrence. However, the recurrence could not be attributed to the fragmentation, as the defect was lateral to the margin of the mesh.

Of the 20 cases in which stainless steel was employed, postoperative complications were few. One case in which two sheets of mesh were employed required removal of the mesh and skin grafting. This case has been included under the recurrences. Frank wound sepsis delaying convalescence, but with ultimate satisfactory result, occurred in another case. Serous collections occurred in the wounds of 2 cases which were troublesome but apparently not detrimental to the result. Pain in the region of the implanted mesh persisting after 19 months was also observed in 1 case. Of the 9 cases in which tantalum was employed there was one persistently painful scar.

Observations on the fibrous reaction to the mesh implanted in the 24 clinical cases are too few to warrant more than passing comment. The one recurrence following use of tantalum was reoperated upon after 11 months. The encasing fibrosis, as well as the infiltration of fibrous tissue into the mesh, made its removal difficult. Two recurrences in the stainless steel group were reoperated upon at 5 months and at 12 months following operation. In both cases, the mesh was removed and replaced by other larger sheets to cover the lateral defects. As with the tantalum, the removal of the stainless steel was difficult because of the fibrosis encasing the mesh as well as that infiltrating the mesh. An accurate comparison of the fibrosis in these 3 cases cannot be made as they were different cases operated upon at different times, but no obvious differences were noted.

## DISCUSSION

Experimental observations comparing tantalum and stainless steel mesh in the dog have recently been reported by Koontz and Kimberly.[4] The material and the methods employed by them were almost identical to ours except that they used a larger number of dogs—76 as compared to 16 in our series. They found in the majority of dogs that the fibrosis was denser on the tantalum side than it was on the stainless steel side. In contrast we found no grossly observable differences in 12 of the 16 dogs in our series, whereas in the remaining 4 dogs a denser fibrosis occurred on the side where the stainless steel mesh had been implanted; yet the infiltration of fibrous tissue into the mesh in these 4 dogs was less than that on the side where tantalum had been implanted. Likewise, the degree of hyalanization and fibroblastic proliferation in 2 of these dogs as seen microscopically was greater around the stainless steel than it was around the tantalum. There was no typical granulomatous or foreign body reaction in any of the four sections studied.

The relationship of a greater or lesser degree of fibrosis accompanying the implantation of wire mesh to the ultimate result of hernia repair is difficult to assess. Further observations will be necessary. Since scar tissue is notably inelastic, its presence alone can hardly insure a satisfactory hernia repair. Yet it may augment the support provided by the framework of the wire mesh.

Since fragmentation of both stainless steel and tantalum mesh occurred in all of the dogs in our series observed six months or longer, it is conceivable that this will occur in many of the clinical cases. This phenomenon was observed in 2 of our cases, once with tantalum and once with stainless steel. In the latter case recurrence was attributed to the fragmentation, as it had taken place in the central portion of the mesh. With this exception, the remaining four recurrences can be attributed to faulty technic. In 3 cases the sheets of mesh employed were too small to adequately cover the defects; in the other, two sheets of mesh were overlapped causing necrosis and sinus formation.

Results considered satisfactory were obtained with either stainless steel or tantalum mesh in the repair of 24 of the 29 hernias. Our observations fail to reveal that one type of mesh is superior to the other. Admittedly, the material on which our observations are based is too limited and the period of follow-up is

too short to allow any final conclusions. It is hoped that further experimental and clinical evaluation of these and other materials will more clearly demonstrate the advantages of one material over those of another.

SUMMARY

Observations on 16 dogs and 24 patients who had implantation of stainless steel and/or tantalum mesh for hernia repair are recorded.

Within the limits of our observations, no apparent differences were noted in the effects produced by these two types of mesh in most of the cases.

Differences in the density of fibrosis associated with the implantation of stainless steel and tantalum were noted in a few of the cases. The significance of these observations are questionable.

Fragmentation of both types of mesh occurred with equal frequency in the dogs and also occurred in 2 of the clinical cases.

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# GROSS BLEEDING FROM THE ALIMENTARY TRACT IN INFANTS AND CHILDREN

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Hematemesis, melena and the passage of blood per rectum by infants and children should be considered serious until proved otherwise. Hematemesis and melena, except when due to blood swallowed from a supra-esophageal source, is seldom insignificant. Rectal bleeding deserves evaluation equally even though most frequently it is not due to a serious disorder.

Five infants and children admitted to the hospital within three weeks time because of hematemesis or rectal bleeding led to a review of our experience in the period from Jan. 1, 1950 through June 30, 1953. Eight additional cases were found. These did not include, with 1 exception, those patients in whom there were hemorrhagic or purpuric manifestations outside the alimentary tract. Thus, patients having hemophilia, leukemia and purpura were excluded. Similarly excluded from consideration were those cases associated with bacterial enterocolitis, chronic ulcerative colitis and poisons. No peptic gastric or duodenal ulcers, intestinal duplications, polyps or polyposis were recognized in this period.

Table I lists the 13 patients with presenting complaints and final diagnoses. This small experience, in itself, scarcely warrants reporting. Since the majority of such patients, however, are seen, at least initially, by physicians or surgeons without a continual and considerable experience with alimentary tract bleeding in the pediatric range, it seems desirable periodically to reconsider this problem.

True hematemesis implies a bleeding site proximal to the first part of the jejunum. Melena is usually, but not always, a concomitant finding. It is possible with systemic blood disorders to have bleeding points scattered throughout the gastrointestinal tract so that both hematemesis and the passage of red blood per rectum may occur. Although melena or bright red blood in the feces without blood in the stomach suggests a source distal to the first portion of the jejunum; bleeding varices and peptic ulcers demand first consideration in the differential diagnosis. In addition to spurious melena due to iron or bismuth medication it should be remembered that acute iron poisoning (ferrous sulfate) may manifest gastrointestinal bleeding. Also patients who have corrosive esophagitis and gastritis due to acids, alkalis, phenols, and mercuric chloride may develop hematemesis and melena.

Table II lists possible causes of hematemesis, melena and rectal bleeding in infancy and childhood.

*Neonatal alimentary tract bleeding.* Even though most bleeding in the newborn period is attributed to hemorrhagic disease of the newborn, it is probably best to consider hematemesis and melena in the newborn period as indicating acute peptic ulcer until proved otherwise.

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TABLE I

| Case | Age | Sex | Presenting Complaint | Diagnosis |
|---|---|---|---|---|
| 1 | 2 days | M | Bloody stools | Alimentary tract bleeding—idiopathic |
| 2 | 3 weeks | F | Colic, bloody stools | Alimentary tract bleeding—idiopathic |
| 3 | 10 months | M | Spots of blood in stools | Food allergy (?) |
| 4 | 3 years | F | Vomiting blood | Esophageal varices, absence of splenic vein |
| 5a | 9 months | M | Bloody stools | Meckel's diverticulum |
| b | 20 months | M | Bloody stools | Alimentary tract bleeding—idiopathic |
| 6 | 7 months | F | Colic, diarrhea, bloody stools | Meckel's diverticulum |
| 7 | 2½ years | M | Passage of blood clots, meningitis | Ulcer, Meckel's diverticulum, Intussusception |
| 8 | 2½ years | M | Bloody stools, cramps after eating, diarrhea | Intussusception, lymphosarcoma of ileocolic valve |
| 9 | 8 months | M | Bloody stools | Alimentary tract bleeding—idiopathic |
| 10 | 3 years | F | Blood in stools, epistaxis, easy bruising | Anal fissure |
| 11 | 5 months | F | Cramps, passage of bright red blood | Intussusception |
| 12 | 22 months | M | Bloody diarrhea, abdominal pain | Intussusception |
| 13 | 4 months | F | Cramps, vomiting, bloody stools | Intussusception |

TABLE II

*Causes of hemathemesis, melena and rectal bleeding*

Swallowed blood—during birth, nursing or after local trauma
Esophageal varices
Peptic ulcer: Duodenal, gastric, esophageal: idiopathic; secondary to sepsis, marasmus, extensive burns, central nervous system pathology
Intestinal duplication
Intussusception, volvulus, incarcerated hernia
Meckel's diverticulum, other diverticulitis
Regional enteritis
Polyps—polyposis
Chronic ulcerative colitis; amoebic, tuberculous, shigella and salmonella enterocolitis
Food allergy
Anal fissure, haemorrhoids, trauma from foreign body (esophagus to anus)
Esophagitis, gastritis: idiopathic or secondary to corrosive agents
Neoplasms along alimentary tract
Bleeding disorders:
  Purpuras: nonthrombocytopenic (Henoch's and other); thrombocytopenic
  Hypoprothrombinemia: hemorrhagic disease of the newborn, liver disease, poisons
  Hemophilia, fibrinogenopenia, deficiency of other coagulation factors
  Familial telangiectasia
Scurvy
Spurious—beets, dyes, iron and bismuth medication
Idiopathic

## CASE REPORTS

Case 1. A full term male infant, the product of an uneventful pregnancy and normal spontaneous delivery, passed two meconium stools with grossly recognizable admixed blood on the first day of life. Five subsequent bowel movements, chiefly blood, occurred in the ensuing 24 hours. The child's family history was noncontributory. Physical examination revealed an active, asymptomatic infant. No bleeding sites could be found. There was no significant drop in hemoglobin. Other blood studies, including bleeding and clotting times, clot retraction, prothrombin time and platelet count, were all within normal limits. Endoscopy and roentgenographic studies were not done. Vitamin K had been given to the mother before delivery. Additional aqueous vitamin K was given to the infant on the second day. No further gross bleeding occurred in the neonatal period nor while followed in the next several months.

*Comment:* Rosenfeld and McGrath[13] report that in the newborn as little as 2.6 cc. of swallowed blood may produce tarry stools within 7 to 17 hours after ingestion. This contrasts with the 50 to 100 cc. usually mentioned in adults. Blood swallowed during birth or coincident with nursing, if the mother's nipples are cracked or fissured, should be ruled out. Hemorrhagic disease of the newborn seemed the most likely diagnosis in this infant with the development of bleeding in the first few days of life not of sufficient degree to produce an appreciable drop in hemoglobin, and with the lack of progression or of recurrences of bleeding. The absence of a significant change in the prothrombin time does not support this, however, and the apparent cessation of bleeding after administration of vitamin K may be coincidental. Endoscopy and roentgenographic studies did not seem justified considering the infant's continued good condition. Without these studies, and in view of the above, it seemed best to consider this undiagnosed gastrointestinal bleeding rather than hemorrhagic disease of the newborn.

Case 2. A full term female infant, whose antenatal, natal and family history were noncontributory, developed colic with bloody stools at the age of 3 weeks, having been irritable and having had anorexia for the preceding 7 to 10 days. The infant had been taking an evaporated milk formula during this time. Two hours after passing the first blood containing stool, the infant passed one which appeared to be all blood, and over the next three to four hours had numerous small movements of fecal material with admixed bright and dark blood. The blood was not streaked on the outside of the movements. The infant appeared *fussy*, but not ill. Physical examination failed to reveal a bleeding site, abdominal mass, or other positive findings. There was no laboratory evidence of a blood dyscrasia. The hemoglobin was within normal limits and remained normal. A barium enema and subsequent barium meal study were negative. Endoscopy was not done. There was no further bleeding after the first 24 hours.

*Comment:* A peptic ulcer was suspected, but not demonstrated. No change was made in this infant's feeding. The family history was negative for allergy, and no bleeding subsequently made a diagnosis of gastro intestinal allergy as a cause of this bleeding untenable. Rubin[14] has described a syndrome in cow's milk fed babies with an allergic family history which consists of hunger, colic, satisfactory weight gain and passage of bowel movements flecked with bright red blood. Rarely, the bleeding may be of sufficient quantity to suggest bleeding from a Meckel's diverticulum. The infants reported by Rubin subsequently developed eczema or asthma. Failure to demonstrate other possible cases as noted in table II left this case also undiagnosed.

Case 3. A 10 months old male infant was admitted to the hospital with a history of four days of rectal bleeding which was described as *little spots mixed in* the feces. This infant, who had a bilaterally positive family history of allergies, had shown a good appetite and satisfactory height-weight progress despite a continuous history of loose bowel movements and colic since birth. Physical examination and laboratory studies were within normal limits. A barium enema and proctoscopic examination failed to reveal any possible source of bleeding. Following elimination of milk from the diet there was no further bleeding,

colic or loose bowel movements. A brief return to milk resulted in the development of an eczematoid rash.

*Comment:* It was believed that this infant's course *fits* the syndrome described by Rubin.

*Hematemesis.* Hematemesis may result from bleeding proximal to the first portion of the jejunum. Esophageal varices as the source of blood should especially be considered past the neonatal period when the possibility of swallowed blood or a peptic ulcer has been ruled out.

Case 4. A 3 year old female, with a past history of repeated severe hematemesis from the age of 7 months, was admitted to the hospital for investigation. There were eight episodes about three months apart. Melena only occasionally was associated. Endoscopic and roentgenographic studies elsewhere were reported as unrevealing, although she had an episode of hematemesis after one esophagoscopy. Laparotomy done in another community was reported to have shown an intestinal hemangioma and a Meckel's diverticulum. The family history was noncontributory. The past history was otherwise unrevealing. There was no history of omphalitis or of infectious diarrhea in infancy. Positive findings at the time of admission were an increased venous pattern over the upper abdomen and lower chest, and liver and spleen palpable 4 centimeters below the costal margins. Laboratory findings revealed a hemoglobin of 12 grams per cent, leukocyte count of 3400 with a differential count of 55 neutrophils and 45 lymphocytes, and a platelet count of 76,000. There was poor clot retraction. Liver function studies, including bromsulfalein retention, cephalin flocculation and thymol turbidity all were within normal limits. The prothrombin time was 70 per cent of the control. Total plasma proteins were 6.8 grams per cent. A bone marrow aspirate was interpreted as being consistent with hypersplenism. A roentgenographic study showed esophageal varices (fig. 1). At operation, no normal portal or splenic venous structures could be found. The major portion of the splenic outflow appeared to be through multiple splenic adhesions to the posterior abdominal wall and diaphragm. Splenectomy was done; a shunt was not feasible. A section of liver taken at the time of operation showed no changes.

*Comment:* Neither the original operative specimen nor sections of the intestinal hemangioma were available. It seems unlikely that the repeated hematemeses had been associated with a Meckel's diverticulum. The splenomegaly and hematemeses strongly suggested portal hypertension. The early onset of hematemeses suggested that this probably was due to to extrahepatic portal obstruction. The postesophagoscopy hemorrhage in this child should have been suggestive of the correct diagnosis. No further hematemeses have occurred in the nine months since the time of the splenectomy.

Esophageal varices imply portal hypertension. It is important to ascertain whether obstruction is hepatic or extrahepatic since splenectomy offers little in the former. Intrahepatic obstruction usually is a part of hepatic cirrhosis, but may occur with primary or metastatic hepatic malignancy.[17] Liver function should be assessed at least by determination of bromsulfalein excretion. The occurrence of ascites or the finding of spider hemangiomata suggest cirrhosis. If no liver dysfunction is demonstrable, then extrahepatic portal obstruction is a reasonable possibility.

Extrahepatic obstruction may be of the portal or splenic veins or both. It may be congenital or acquired as a result of thrombophlebitis or secondary to external pressure. Smith and Farber[15] pointed out that splenomegaly may be negligible immediately after severe hematemesis, only to recur when the blood volume is restored. This may be deceiving in that it may remove portal hypertension from consideration. They further state that those with early hematemesis and normal peripheral blood seldom progress to cirrhosis and ascites. The children with nonpalpable spleens and sudden hematemesis may simply present a picture of *a well child with hematemesis*. These children should not be operated upon with the misdiagnosis of peptic ulcer. The lower third of the esophagus should be

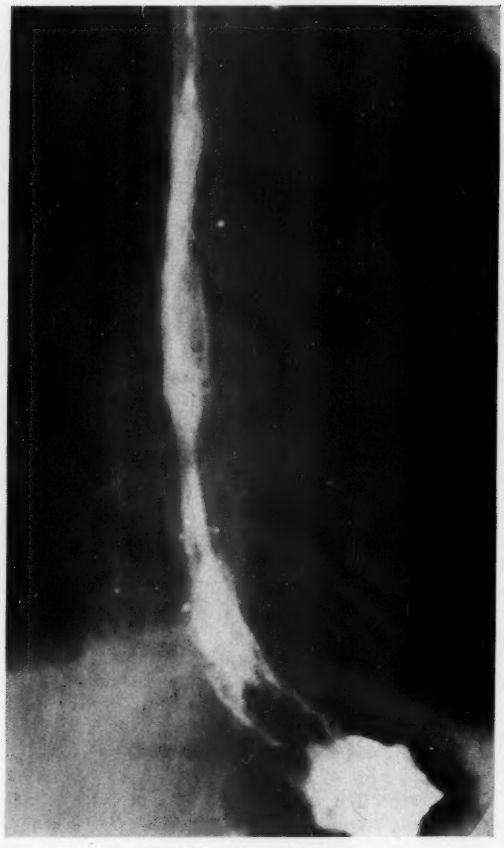

FIG. 1. Esophagram showing varices.

visualized by thick barium or endoscopy in those cases of hematemesis where the diagnosis is not otherwise completely clear.

In the presence of splenomegaly and portal hypertension, anemia and various cytopenias may occur. Study of the peripheral blood and bone marrow may be necessary to rule out primary blood dyscrasias.

*Peptic ulcer.* Acute peptic ulcers appear to be more frequent than chronic peptic ulcers in infancy and early childhood. Duodenal ulcers are reported as being more frequent than gastric ulcers by a ratio of from 2:1 to 5:1. Kennedy[9] suggested that peptic ulcer be considered in three groups: those occurring in the neonatal period; those from two weeks to one year; and chronic peptic ulcer in childhood. This division remains of practical value. Bird, Limper and Mayer[2] reviewed 245 cases of peptic ulcer in childhood and infancy including 119 with surgical intervention. An increasing number have been recognized since that time.

In the newborn and in early infancy, peptic ulcer usually is acute and fre-

quently is first manifested by hemorrhage or perforation. In the neonatal period hematemesis and melena are equivalent to the diagnosis of peptic ulcer until proved otherwise. Although most peptic ulcers in this period are not diagnosed until autopsy; an increasing number are being diagnosed antemortem and operated upon with survival.

Cole[3] and Hollander and Stark[7] stress that the signs and symptoms of pyloric stenosis in an infant beyond the ages of 2 to 4 months well may be due to peptic ulcer, particularly duodenal ulcer. Hematemesis seems to be less frequent than melena in this period.

Girdany's[4] experience suggests that peptic ulcer may be much more frequent in childhood than usually has been appreciated. In this age group hematemesis and melena is not a prominent feature. Recurrent abdominal pain, cyclic vomiting or vomiting without pain may occur as the principal manifestations of peptic ulcer in this age period. The usual adult symptomatology is more frequent after the age of 9 years.

*Meckel's diverticulum.* Moses[12] reported that hemorrhage was the presenting complaint in 30 per cent of Meckel's diverticula coming to medical attention. Intussusception and intestinal obstruction were present in 23 per cent, while perforation occurred in 13.8 per cent. Sudden, severe, silent rectal bleeding occurring at relatively long intervals suggests ulceration associated with a Meckel's diverticulum. The first movements may be tarry and subsequent passages may contain bright red clotted or unclotted blood. Occasionally an anal fissure or rectal polyp may be suggested by the repeated passage of small quantities of bright red blood. Roentgenologic studies are seldom useful in the diagnosis of Meckel's diverticulum.

Bright red or dark blood usually well mixed in the feces suggests a source in the small intestine. The absence of hematemesis and failure to find bleeding on passage of a stomach tube further supports this suggestion. Meckel's diverticulum, intestinal duplication and polyposis should all be considered. Blood and vascular disorders must be ruled out. When associated with pain, similar bleeding per rectum suggests intussusception or other obstructive conditions, including volvulus and strangulated hernia. Anaphylactoid purpura (Henoch's may not be distinguishable from intussusception preoperatively.

Case 5. This male infant was first seen at the age of 9 months because of painless bloody stools for two weeks before admission to the hospital. These stools were noted as being dark reddish-brown blood mixed with feces. The bleeding was sufficient to require three blood transfusions. The past history and family history were noncontributory. Physical examination was negative except for slight pallor. Laboratory: The hemoglobin was 9.5 Gm. per cent on admission and 6.3 Gm. per cent three days later. Other studies were normal. A barium enema and proctoscopic examination were negative. Laparotomy revealed a Meckel's diverticulum which was excised. An ulcer crater was found within the diverticulum.

The child was readmitted to the hospital two months later because of postoperative small bowel obstruction. This was surgically relieved. He was admitted a third time at the age of 20 months because of periodic episodes of rectal bleeding, dark in nature, for the preceding seven months, and with recent bright red rectal bleeding. The physical examination was negative. Laboratory examinations were significant only in that the hemoglobin

was 7.5 Gm. per cent. Roentgenographic examination, including a gastrointestinal series, barium enema, and proctoscopic examination were negative. Laparotomy was not done. No further bleeding occurred in the subsequent six months after which time he was lost from follow-up.

*Comment:* The finding of an ulcer associated with Meckel's diverticulum on the first admission confirmed the expected diagnosis. The recurrence of rectal bleeding, especially varying from dark to bright red, suggested the possibility of bleeding from an intestinal duplication or intestinal or colonic polyposis. Failure to recognize either of these conditions by roentgenographic studies does not rule them out. Proctoscopic examination should reveal rectal or sigmoidal polyps.

*Duplication of the alimentary tract.* Gross[5, 6] comments on the increasing frequency with which these anomalies are being reported. Duplications may be found from the esophagus to the rectum. They may present themselves because of pain, obstructive phenomena or bleeding. Hematemesis may result from esophageal or duodenal duplications. Bleeding per rectum may follow esophagic, duodenal or lower intestinal tract duplications. These anomalies may be recognized roentgenographically as radiopaque areas displacing the usual gas pattern. Occasionally roentgenographic study with contrast media may reveal abnormal filling.

Case 7. A 2½ year old male was referred with a provisional diagnosis of meningitis and coincident rectal passage of dark blood clots without apparent abdominal pain. The illness started 24 hours before admission to the hospital with fever, drowsiness and stiffness of the neck. The morning of admission several bowel movements with small quantities of admixed clotted blood were noted. The child's past history and family history were negative.

*Physical examination:* The temperature was 39.4 C., rectally. There was questionable meningismus, otherwise the examination was negative. Laboratory work revealed a hemoglobin of 8 Gm. per cent and a hematocrit of 26. The leukocyte count was 42,000 with 87 per cent polymorphonuclears, and 13 per cent lymphocytes. Further blood studies revealed no evidence of a dyscrasia. Spinal fluid examination was negative. Proctoscopic examination was negative as was the barium enema. Under fluoroscopy, after a small barium meal, a filling defect was noted in the terminal ileum. This provisionally was diagnosed as being an ileal polyp. Laparotomy revealed a Meckel's diverticulum which served as the leading point of a nonreducible intussusception. Resection of the diverticulum and this portion of the bowel revealed, in addition, an ulcer within the diverticulum. No ileal polyp was found.

Case 8. A 2½ year old male was referred with a history of four or more weeks diarrhea, moderate vomiting and abdominal cramps occurring some 15 to 20 minutes after eating. Two weeks before admission to the hospital the child had passed dark and fresh blood and mucus in the stool. During this time he had up to 20 small bowel movements per day. The physical examination was negative. Laboratory studies revealed a hemoglobin of 11 Gm. per cent and a normal white count. The platelets were 47,000 but with normal clot retraction. Bleeding and clotting times were normal. Roentgenographic examination showed an ileocolic intussusception. At operation the intussusception was found to have been reduced, but there was a small mass at the ileocecal valve. This was resected and subsequently diagnosed as lymphosarcoma. No evidence of metastases were found in the regional nodes removed at operation. No roentgenotherapy was given. The child was readmitted two months later with history of bloody bowel movements for four days and abdominal distention due to ascites. The child died three weeks later. Autopsy showed lymphosarcoma throughout the abdominal and thoracic cavities.

*Comment:* The experience with these last 2 children argues strongly for laparotomy in cases of alimentary tract bleeding whether or not obstruction is suspected or demonstrated.

Earlier conservatism seems less warranted in view of the advances in anesthesiology, operative technic and preoperative and postoperative care.

*Intussusception.* The sudden onset of excruciating, abdominal colic in a previously healthly infant, recurring at intervals with associated vomiting and the subsequent passage of mucoid bloody material per rectum is most suggestive of intussusception. Palpation of an abdominal mass, emptiness of the right lower quadrant or a cervical-like mass felt on rectal examination further support the diagnosis. The incidence of rectal bleeding is variously reported. Lawrence and Ulfelder[11] reported no rectal bleeding in half of their patients. Bleeding may be noted, however, in more than half of the patients varying from a mere bloody discharge to massive hemorrhage. Tumors, polyps and Meckel's diverticulum are more frequently associated with intussusception in those patients beyond infancy.

Hydrostatic reduction of intussusception is gaining increasing favor. This may be satisfactory in a relatively early intussusception in infancy, but a barium enema given for other reasons than diagnosis of an intussusception cannot be relied upon to show polyps or diverticula.

Case 9. This 8 month old male, while hospitalized because of diarrhea due to Shigella paradysenteriae, developed black liquid stools. Evaluation of the infant at this time, including search for evidence of a blood dyscrasia and roentgenographic contrast study of large and small bowel and sigmoidoscopy, gave no explanation of the cause of the condition. Subsequently the infant went into shock after two voluminous bloody bowel movements. After restoration of circulation by transfusion, a laparotomy failed to reveal the source of bleeding. The examination at operation extended from the cardia to the rectum. No further bleeding occurred in the following seven months.

Case 10. A 3 year old girl was referred to the Colorado General Hospital because of frequent epistaxes, easy bruising and bright red blood streaked on the outside of stools. Inquiry revealed that she was chronically constipated and intermittently had painful bowel movements. Examination revealed no abnormalities except a small anal fissure. Laboratory studies were within normal limits. Sigmoidoscopy was negative. Following introduction of a mild laxative regimen no further rectal bleeding occurred.

*Comment:* These last 2 cases raised the possibilities of polyps, intestinal duplication, blood dyscrasias, as well as simple constipation and anal fissure. The patient in case 9 was not severely ill with shigellosis. It did not seem that ulcerations associated with sepsis were likely. No note was made as to the upper limit of blood in the intestine. It is possible that exposure of the bowel lumen at the bleeding site may reveal a bleeding point such as a telangiectatic area. The patient in case 10 seemed obviously a simple problem of constipation, fissure in ano and painful defecation. The story of epistaxes and easy bruising, however, justified consideration of a less obvious diagnosis.

*Polyps and polyposis.* Polyps may be single or scattered or as multiple polyposis from rectum to upper small intestine. Kennedy[10] noted that they seldom cause symptoms under 1 year of age, but are most common between the ages of 4 and 6 years. Single or multiple rectal polyps are frequent. Polyps may come to medical attention with one or several of the following symptoms: diarrhea, abdominal pain, anal mass or intermittent passage of blood rectally. Bleeding may vary from occasional bright red streaking on the outside of bowel movements to several ounces of dark red or tarry material. The absence of severe bleeding should not lessen one's concern. These lesions are subject to malignant changes.

Jeghers, McKusick and Katz[8] described a syndrome with symptoms of recurrent small intestinal intussusception accompanied by occasional variable quantities of melena in patients with melanin spots on the lips, oral mucosa, fingers and toes and with jejunal or generalized intestinal polyposis. There appears to be a familial tendency in such cases.

Even though bright red blood not mixed with the feces is most often due to an anal fissure, polyps and foreign bodies must be considered and ruled out. Digital rectal examination, proctoscopy and roentgenographic study, especially double contrast enemas, should be done.

Pus and mucous in the bowel movement, in addition to blood, suggests enterocolitis. Shigella, salmonella, tuberculous, amoebic ulcerations, and chronic ulcerative colitis must be considered and eliminated by appropriate studies. Regional enteritis, also, may occasionally cause rectal bleeding or melena.

*Coagulation and vascular disorders.* Anaphylactoid purpura (Henoch's) may simulate or lead to intussusception. Bailey[1] states that both may induce signs and symptoms of intestinal obstruction as well as a palpable abdominal mass. Even the presence of extra-abdominal purpuric manifestations does not permit a *hands-off* policy. The symptomatic nonthrombocytopenic purpuras associated with infections and poisons, similarly may be confusing. Thrombocytopenic purpura, idiopathic or secondary to leukemia, infections, and poisons usually will present other purpuric phenomena beyond alimentary tract bleeding. A low platelet count, poor clot retraction, and prolonged bleeding time quickly should lead to a proper provisional diagnosis and subsequent definitive studies.

Hypoprothrombinemia may be encountered in various conditions. The reader is referred to Stefanini's[16] unusually clear discussion of the various factors concerned in blood coagulation. Hemorrhagic disease of the newborn generally seems to be considered the prime cause of bleeding in the neonatal period. This is true despite the fact that many so diagnosed do not show an abnormal prothrombin time. It should be remembered that hypoprothrombinemia may occur not only from dicumarol, but also in salicylism and in poisoning with the rodenticide, Warfarin.

Familial hemorrhagic telangiectasia is most frequently manifested as repeated epistaxes. The pinpoint to split pea size telangiectases may occur, however, anywhere on the skin or mucous membranes and lead to repeated bleeding from these sites. Failure to directly visualize the intestinal mucosa at the upper level of bleeding will result in such lesions being missed.

## SUMMARY

Although severe protracted alimentary tract hemorrhage occasionally may warrant immediate surgical intervention, the systematic consideration of the possibilities listed in table II is almost always both possible and wise after restoration of the circulating blood volume.

Bleeding due to vascular or coagulation disorders should be considered even though another cause may seem more evident.

Investigation of hematemesis is not complete without an esophageal flu-

oroscopic and roentgenographic visualization with thick barium. In mid-intestinal tract bleeding roentgenographic studies may be diagnostic, but laparotomy, including localization of the upper limit of bleeding and direct visualization of the mucosa at that level, may be necessary. Negative roentgenographic or endoscopic study does not eliminate the need for laparotomy.

At the present time, in hospitals offering the benefits of advances in preoperative and postoperative care, anesthesia and operative technic, the earlier reluctance to expose infants and children to surgery does not seem justified.

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